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Award Number: DAMD17-03-1-0354

TITLE: Exploring Early Detection Methods: Using the Intraductal Approach to Predict Breast Cancer

PRINCIPAL INVESTIGATOR: Kimberly Baltzell, Ph.D.

CONTRACTING ORGANIZATION: University of California
San Francisco, CA 94143

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University of California
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Abstract is on page 4 of the report.

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breast fluids, breast cancer risk, nipple aspiration, ductal lavage

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Abstract

Breast cancer is a leading cause of death among women in the U.S. Early diagnosis is believed to be key to minimizing mortality, thus, techniques to identify high-risk women are essential. This study is using an interdisciplinary approach to conduct a follow-up study on a group of 3413 women from the Santa Barbara, Ca area who had breast fluids drawn between 1970-1990 using one of the following three methods: nipple aspiration, ductography or ductal lavage. The follow-up study will determine if abnormal cytologic findings from the past are associated with a higher incidence of breast cancer development during the later years. Follow-up methods include direct contact using questionnaires, linkage with the California Cancer Registry (CCR), linkage with the California Department of Vital Statistics and the National Death Index. As of 5/04, the CCR has yielded information on 344 subjects, with a total of 386 tumors. The study hypothesis is that women with abnormal cytologic findings in breast fluid will be 2.0 - 5.0 times more likely to develop breast cancer than women with normal cytologic findings or women from whom no fluid could be obtained.

2005 Annual Summary Report for Award # DAMD17-03-1-0354
Exploring Early Detection Methods: Using the Intraductal Approach to Predict Breast Cancer

INTRODUCTION:

Nipple aspiration, ductal lavage and ductography are methods of obtaining breast fluids from women who are neither pregnant or lactating. Breast cells in these fluids can be classified as either normal or as showing various abnormalities including hyperplasia, atypical hyperplasia and cancer. In previous follow-up studies of women who participated in breast fluid and tissue studies, it was shown that women with proliferative cytology (hyperplasia or atypical hyperplasia) were significantly more likely to develop breast cancer than women with normal cytologic findings in breast fluids or than women from whom fluid could not be obtained. (Fabian et al., 2000; Wrensch et al., 2001) This study is following an additional cohort of women from Santa Barbara, CA that had fluids drawn between 1970-1990. Statistical methods of association will be used to determine if women with abnormal ctyologic findings developed breast cancer at a higher rate than women with normal cytologic findings or women from whom fluid could not be obtained.

BODY:

The stated goals in the Statement of Work shall be addressed below:
Step 1 – A brief review of the 2004 annual summary will be given. The research team met approximately once every 2 weeks during the first year of the study. During this time, both subject and proxy questionnaires were designed to collect information on pertinent variables for the study. The data set was reviewed for duplicate entries and set up in Access. Approval was received from the UCSF IRB for the questionnaires designed. Kimberly Baltzell finished her required course work and passed her qualifying exams on September 9, 2003.

Step 2 - A computer tracking database has been set up for the 3140 potential subjects. Jennette Sison, MPH from the UCSF Department of Neurological Surgery has been identified as a potential study coordinator once data collection begins. Kimberly Baltzell has been corresponding with Dr. Inese Beitins from the DOD to establish final human subjects approval for this study. On March 24, 2005, contingent approval was received from the DOD for the study, pending final IRB approval from UCSF. Information sheet and questionnaire revisions requested by the DOD have been submitted to the UCSF IRB for approval. Contingent approval was received on May 19, 2005 and the final report has been sent to the UCSF IRB. Final approval is anticipated within 2 weeks of this report date. Once the UCSF IRB final approval has been received, it will be sent to Dr. Beitins at the DOD for final DOD human subjects approval. At this point, the UCSF team will be free to begin subject contact and initiate the study.

Steps 3-5 – Due to the human subjects issues, these steps in the study have been delayed as they involve direct contact with subjects. A request for a no-cost extension for this grant was sent to Ms. Rita Johnson with the DOD in May, 2005. We are waiting for a response at this time.

While pursuing human subjects approval, Kimberly Baltzell has written and published 2 journal articles relevant to the subject matter of this proposal (Baltzell, Eder, & Wrensch, 2005; Baltzell & Wrensch, 2005). The articles are referenced below under Reportable Outcomes. In addition to the published articles, another article exploring characteristics associated with obtaining nipple aspirate fluid has been submitted for review to Cancer, Epidemiology, Biomarkers and Prevention.

KEY RESEARCH ACCOMPLISHMENTS:

Due to the human subjects concerns listed above, there has been no data collection, therefore no data analysis is available at this time.

REPORTABLE OUTCOMES:

-poster presentation: Oncology Nursing Society – Anahem, CA, April 2004 (see attached abstract)

- article – Breast Carcinogenesis – Can the Examination of Ductal Fluid Enhance Our Understanding? ONF, January 2005

- article – Strengths and Limitations of Breast Cancer Risk Assessment. ONF, May 2005

- article – Variables Associated with Obtaining Nipple Aspirate Fluid in a Cohort of Non-Lactating Women. Submitted to Cancer, Epidemiology, Biomarkers and Prevention, April, 2005.

CONCLUSIONS:

This section is not applicable at this time.

REFERENCES:

See attached.

Prepared by Kimberly Baltzell
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Fax: 415-435-5187
kbaltzell@earthlink.net

References

Baltzell, K., Eder, S., & Wrensch, M. (2005). Breast carcinogenesis - Can the examination of ductal fluid enhance our understanding? *Oncology Nursing Forum, 32*(1), 33-39.

Baltzell, K., & Wrensch, M. (2005). Strengths and Limitations of Breast Cancer Risk Assessment. *Oncology Nursing Forum, 32*(3), 605-616.

Fabian, C. J., Kimler, B. F., Zalles, C. M., Klemp, J. R., Kamel, S., Zeiger, S., et al. (2000). Short-term breast cancer prediction by random periareolar fine-needle aspiration cytology and the Gail risk model. *Journal of the National Cancer Institute, 92*(15), 1217-1227.

Wrensch, M. R., Petrakis, N. L., Miike, R., King, E. B., Chew, K., Neuhaus, J., et al. (2001). Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. *Journal of the National Cancer Institute, 93*(23), 1791-1798.

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University of California
San Francisco

Susan Love M.D. Breast Cancer Research Foundation

Exploring Early Detection Methods: Using the Intraductal Approach to Predict Breast Cancer Risk

Dr. Otto Sartorius' Breast Clinic Follow-up Study

1. Purpose, Participation and Procedures

You are invited to participate in this research study because your (*relationship to deceased*) had breast fluid specimens evaluated by Dr. Sartorius between 1970 and 1990. Marylin Dodd, RN, PhD and Kimberly Baltzell, RN, PhD (c) (1-800-XXX-XXXX) in the Department of Physiological Nursing, UCSF, Margaret Wrensch, PhD in the Department of Neurological Surgery at UCSF and the Susan Love MD Breast Cancer Foundation are conducting the study.

This study will determine breast cancer occurrence in women who participated in breast fluid studies with Dr. Otto Sartorius between 1970 and 1990. The purpose is to decide if women who had abnormal cells in breast fluid specimens were more likely to develop breast cancer than women with normal cells in breast fluid specimens or than women from whom fluid could not be obtained.

If you agree to participate in the study, you will do the following:
1) Fill out the enclosed questionnaire and return it to the investigator in the post-paid envelope. The questionnaire will take approximately 30-45 minutes to complete.
2) You can also participate in the study by calling 1-800-XXX-XXXX for a telephone interview.

You are free to decline to answer any questions

2. Description of Risks

The risk from this study is that you may feel some discomfort at recalling your (*relationship's*) medical history. Participation in research may involve a loss of privacy, but information about your (*relationship to deceased*) will be handled as confidentially as possible.

3. Confidentiality

Your (*relationship to deceased*) will not be used in any published reports about this study. Study information will be coded and kept in locked files at all times. Only study personnel will have access to your (*relationship to deceased*) files. Representatives of the U.S. Army

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Medical Research and Material Command are eligible to review research records as part of their responsibility to protect human subjects in research.

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4. Benefits

There is no direct benefit to you from participating in this study. The anticipated benefit from this study is confirmation that nipple aspirate fluid (cellular studies) may be a useful tool in addition to other screening methods to identify women who may be at high risk of breast cancer.

5. Alternatives

An alternative is not to participate in the study.

6. Compensation

There is no compensation for participating in this study.

7. Treatment for Injury

There is no medical treatment available for participants in this study.

8. Potential Conflict of Interest and Funding

The researchers conducting this study do not have any known financial interests that may affect the performance or interpretation of this research. Funding for this study has been provided by the Department of Defense, Breast Cancer Research Dissertation Award #BC021862.

9. Questions

If you have any questions or comments about participating in this study, you should first talk with Dr. Marylin Dodd or Kimberly Baltzell, RN, PhD (c) at 1-800-XXX-XXXX. If for some reason you do not wish to do this, you may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. You may reach the Committee office between 8:00 a.m. and 5:00 p.m. Monday-Friday, by calling 415-476-1814, or by writing to the Committee on Human Research, Suite 11, Laurel Heights Campus, Box 0962, University of California, San Francisco, CA 94143.

10. Consent

Enclosed please find a copy of the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without jeopardy to your present or future status as a patient at UCSF.

Participant's Signature **Date**

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Enclosures.
Patient Info sheet – proxy
ATTACH MEMID STICKER BEFORE MAIL-OUT

Updated/Revised: 03/22/2005 by JDS

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University of California
San Francisco

Susan Love M.D. Breast Cancer Research Foundation

University of California, San Francisco
Research Study Information Sheet
Sartorius Follow-up Study

A. Purpose and Background

You have been asked to participate in this research study because you had breast fluid specimens evaluated by Dr. Sartorius between 1970 and 1990. Dr. Sartorius collected nipple aspiration specimens as part of his standard clinical assessment. There was no original study outlined or intended at the time of the breast fluid collection. Researchers now believe that following up on this information may be important and are requesting your consent at this time. This study is being conducted by Marylin Dodd, R.N., Ph.D. and Kimberly Baltzell, R.N. (1-800-XXX-XXXX) in the Department of Physiological Nursing, UCSF, Margaret Wrensch, PhD in the Department of Neurological Surgery at UCSF and the Susan Love MD Breast Cancer Foundation.

This study will determine breast cancer occurrence in women who participated in breast fluid studies with Dr. Otto Sartorius between 1970 and 1990. The purpose is to decide if women who had abnormal cells in breast fluid specimens were more likely to develop breast cancer than women with normal cells in breast fluid specimens or in women from whom fluid could not be obtained.

B. Procedures

If you agree to be in this study, you will do the following:
1) Fill out the enclosed questionnaire and return it to the investigator in the post-paid envelope. The questionnaire will take approximately 30-45 minutes to complete.
2) You can also participate in this study by calling 1-800-XXX-XXXX to arrange for a telephone interview.

You are free to decline to answer any questions

C. Risk and/or Discomforts

The risk from this study is that you may feel some discomfort at recalling your medical history.

Confidentiality: Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. Your name will not be used in any published reports about this study. Study information will be coded and kept in locked files at all times. Only study personnel will have access to the files. Representatives of the U.S.

Deleted: 11/04/2004

Army Medical Research and Material Command are eligible to review research records as part of their responsibility to protect human subjects in research.

D. Benefits

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There is no direct benefit to you from participating in this study. The anticipated benefit from this study is confirmation that nipple aspirate fluid (cellular studies) may be a useful tool in addition to other screening methods to identify women who may be at high risk of breast cancer.

E. Alternatives

An alternative is not to participate in the study.

F. Costs and Reimbursements

There will be no costs and no reimbursements to you for taking part in this study.

G. Treatment for Injury

There is no medical treatment available for participants in this study.

H. Potential Conflict of Interest and Funding

The researchers conducting this study do not have any known financial interests that may affect the performance or interpretation of this research. Funding for this study has been provided by the Department of Defense, Breast Cancer Research Dissertation Award #BC021862.

I. Questions

If you have any questions or comments about participating in this study, you should first talk with Dr. Marylin Dodd or Kimberly Baltzell,R.N. at 1-800-XXX-XXXX. If for some reason you do not wish to do this, you may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. You may reach the Committee office between 8:00 a.m. and 5:00 p.m. Monday-Friday, by calling 415-476-1814, or by writing to the Committee on Human Research, Suite 11, Laurel Heights Campus, Box 0962, University of California, San Francisco, CA 94143.

J. Consent

Enclosed please find a copy of the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without jeopardy to your present or future status as a patient at UCSF.

Participant's Signature **Date**

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Enclosures.
Patient Info Sheet - living
ATTACH MEMID STICKER BEFORE MAIL-OUT

Updated/Revised: 03/22/2005 by JDS

UCSF
University of California
San Francisco

Susan Love M.D. Breast Cancer Research Foundation

«FNAME» «LNAME»
«UPDADDR»
«UPDCITYST» «UPDZIP»

<< Sent Date>>

Dear Ms. «LNAME»:

We are contacting you because you were seen by Dr. Otto Sartorius in Santa Barbara between 1970 and 1990. We are continuing to study personal and physiological characteristics of Dr. Sartorius' patients with and without breast disease. As a prior patient of Dr. Sartorius, you are invited to participate in this research study. Dr. Sartorius was a pioneering physician who developed innovative procedures to help detect breast disease at early stages. Your participation in our study is very important to breast cancer research. By knowing about your current state of health, we can see if information contained in your records years ago predicts where you are today.

Participation involves filling out and returning the short questionnaire included in this packet. There are no medical procedures. All study information is coded so that your personal identity is not revealed. The computer file that contains your name and address is protected and maintained under strict confidentiality. If we do not receive your questionnaire or postcard in a few weeks, we may contact you by phone in the future.

We assure you that your privacy will be maintained. Your participation in this study is completely voluntary; you may refuse to answer any of the questions. Please contact Kimberly Baltzell, Co-Principal Investigator, or Jennette Sison, Project Coordinator, at **1-800-XXX-XXXX** if you prefer to complete the questionnaire by phone or with any questions you may have regarding the study and/or study materials.

Results from the follow-up study will greatly contribute toward establishing whether the techniques Dr. Sartorius pioneered in the 1970's can predict who might develop breast disease in the future.

Although you may have been contacted in the past several years regarding similar information, please complete the enclosed materials. We are continuing the study and would appreciate your most up-to-date information. Thank you very much for your time and consideration.

Sincerely,

Susan M. Love, M.D.
President and Medical Director
Susan Love MD Breast Cancer Research Foundation

Margaret Wrensch, Ph.D.
Professor
UCSF Dept. of Epidemiology & Biostatistics

Marylin Dodd, R.N., Ph.D.
Associate Dean
UCSF Dept. of Physiologic Nursing

Kimberly Baltzell, R.N., Ph.D.(c)
Study Co-Principal Investigator
UCSF Dept. of Physiologic Nursing

Enclosures.
Patient Intro-letter

Revised: 01/20/2004 by JDS

UCSF
University of California
San Francisco

Susan Love M.D. Breast Cancer Research Foundation

«FNAME» «LNAME»
«UPDADDR»
«UPDCITYST» «UPDZIP»

<<Sent Date>>

Dear Family of Ms. «FNAME» «LNAME»:

We are contacting you because Ms. «FNAME» «LNAME» was seen by Dr. Otto Sartorius in Santa Barbara between 1970 and 1990. UCSF and the Susan Love MD Breast Cancer Foundation are following-up Dr. Sartorius's patients to study personal and physiological characteristics of women with and without breast disease. As the [redacted] prior patient of Dr. Sartorius, you are invited to participate in this research study. Dr. Sartorius was a pioneering physician who developed innovative procedures to help detect breast disease at early stages. Participation in our study is very important to breast cancer research. By knowing about your [redacted] state of health, we can see if information contained in her records years ago predicted eventual health outcomes.

Participation involves filling out and returning the short questionnaire regarding Ms. «FNAME» «LNAME» included in this packet. There are no medical procedures. All study information is coded so that her personal identity is not revealed. The computer file that contains all names and addresses is protected and maintained under strict confidentiality. If we have not received the questionnaire or postcard in 2-3 weeks, we will attempt to contact you by phone.

You may not want to tell us about certain information. We assure you that your privacy and Ms. «FNAME» «LNAME» 's privacy will be maintained at all times. Please feel free to contact Kimberly Baltzell, Co-Principal Investigator, or Jennette Sison, Project Coordinator, at [redacted] if you prefer to complete the questionnaire by phone or with any concerns you may have regarding the study and/or study materials.

Results from the follow-up study will greatly contribute toward establishing whether the techniques Dr. Sartorius pioneered in the 1970's can predict who might develop breast disease in the future.

You or Ms. «FNAME» «LNAME» may have been contacted in the last several years regarding this information. A new research team is continuing the study and the completion of the attached materials would be greatly appreciated. Thank you very much for your time and consideration.

Sincerely,

Susan M. Love, M.D.
President and Medical Director
Susan Love MD Breast Cancer Research Foundation

Margaret Wrensch, Ph.D.
Professor
UCSF Dept. of Epidemiology & Biostatistics

Marylin Dodd, R.N., Ph.D.
Associate Dean
UCSF Dept. of Physiologic Nursing

Kimberly Baltzell, R.N., Ph.D.(c)
Study Co-Principal Investigator
UCSF Dept. of Physiologic Nursing

Enclosures.
Family intro-letter

Revised: 04/01/04 by KB

DR. OTTO SARTORIUS' BREAST CLINIC FOLLOW UP STUDY

University of California, San Francisco
Department of Physiological Nursing
&
Susan Love MD Breast Cancer Research Foundation

If you prefer to complete this questionnaire by phone or have any questions, please call:

1-800-XXX-XXXX

FOR OFFICE USE ONLY:

☐ Completed via phone
DATE:_____ INTVWR: _____

☐ Received via mail

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CONTACT INFORMATION

Please fill in the requested information below in the event that we need to contact you in the future.

Current address: _____

City:_____ State _____ Zip code _____

Home phone number: (__ __ __) __ __ __ - __ __ __ __

Work phone number: (__ __ __) __ __ __ - __ __ __ __

Best time to contact you: _____

If completed by someone other than addressee, please list your name and relationship:

First name _____ Last name _____

Your relation to addressee: _____

In case you move, or we are unable to reach you at the information above, please provide us with the name of a close friend or relative who would know how to contact you.

First name _____ Last name _____

Address of person

on line above: _____

City: _____ State _____ Zip code _____

Phone number: (__ __ __) __ __ __ - __ __ __ __

Relationship to you: _____

FOR OFFICE USE ONLY:

Remove front and back sheet from questionnaire and store in locked file.

Please do NOT put your name on this form ID#

SARTORIUS FOLLOW UP STUDY 2003-2005

University of California, San Francisco
Department of Physiological Nursing
&
Susan Love MD Breast Cancer Research Foundation

Please complete this questionnaire by ***circling or filling in*** the appropriate answers.

DEMOGRAPHIC QUESTIONS

1. Today's date: _____/_____/_____
   month / day / year

2. What is your date of birth? _____/_____/_____
   month / day / year

3. Which number best describes the highest grade or degree that you achieved?
   1 = Less than high school
   2 = High school
   3 = Junior college, Associate's Degree
   4 = Some college, no degree
   5 = Bachelor's Degree
   6 = Master's Degree
   7 = Doctorate Degree
   8 = Other, please specify:_____

4. Please indicate the number that best describes the total pre-tax annual income of all members of your household in 2002.
   0 = Less than $24,999
   1 = $25,000 to $49,000
   2 = $50,000 to $74,000
   3 = $75,000 to $99,999
   4 = $100,000 to $149,000
   5 = $150,000 to $199,999
   6 = $200,000 to $299,000
   7 = $300,000 to $399,000
   8 = $400,000 to $499,000
   9 = $500,000 or more

5. Which number best describes your race or ethnic background?
   1 = Caucasian/White
   2 = Black, African-American
   3 = Chinese-American
   4 = Japanese-American
   5 = Filipina-American
   6 = Mexican
   7 = Other Hispanic or Latina
   8 = Other, please specify:_____

BREAST CONDITIONS AND STATUS

6. Over the past 5 years, have you practiced breast self-examination?
   - 0 = no, never or rarely
   - 1 = yes, less than once every 6 months
   - 2 = yes, about once every 2-6 months
   - 3 = yes, about once every month
   - 4 = yes, more than once a month
   - 5 = other, please specify: _____

7a. Have you ever had breast cancer?
   - 0 = no → ***SKIP TO QUESTION 8***
   - 1 = yes, right breast → Year first found_____
   - 2 = yes, left breast → Year first found _____
   - 9 = uncertain; please explain _____

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7b. How was the first breast cancer found if more than one? (Circle all that apply)
   - 1 = self exam
   - 2 = clinical breast exam
   - 3 = mammogram
   - 4 = ultrasound
   - 5 = biopsy
   - 6 = other, please specify: _____
   - 9 = uncertain; please explain _____

8. Have you ever had a breast lumpectomy (removal of lump or part of breast)?
   - 0 = no, never
   - 1 = yes, right breast → Year procedure was done _____
   - 2 = yes, left breast → Year procedure was done _____
   - 9 = uncertain; please explain _____

9. Have you ever had a mastectomy (removal of entire breast)?
   - 0 = no, never
   - 1 = yes, right breast → Year procedure was done _____
   - 2 = yes, left breast → Year procedure was done _____
   - 9 = uncertain; please explain _____

10. Have you ever had a mammogram?
   - 0 = no, never
   - 1 = yes, less than once every 3 years
   - 2 = yes, about once every 2 years
   - 3 = yes, once a year
   - 4 = yes, more than once a year
   - 5 = yes, other, please specify: _____
   - 9 = uncertain; please explain _____

11. Have you ever had a breast biopsy?
0 = no, never → ***SKIP TO QUESTION 12***
1 = yes, LEFT only ****please COMPLETE Column A in the table below****
2 = yes, RIGHT only ****please COMPLETE Column B in the table below****
3 = yes, BOTH breasts ****please COMPLETE Columns A & B in the table below****
9 = uncertain; please explain _____

*Information about your biopsy results. Please circle whether the "finding" was benign, malignant, or unknown. If the finding was **benign**, please circle hyperplasia, atypia, or unknown.*

COLUMN A – LEFT BREAST			***COLUMN B – RIGHT BREAST***		
	Year of biopsy	Finding (please circle one)		Year of biopsy	Finding (please circle one)
Biopsy #1		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Biopsy #1		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Biopsy #2		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Biopsy #2		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Biopsy #3		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Biopsy #3		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Biopsy #4		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Biopsy #4		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Biopsy #5		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Biopsy #5		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain

If you had more than 5 biopsies, please write the information in question 30.

12. Have you ever had a fine needle aspiration of your breast(s)?
    0 = no, never → ***SKIP TO QUESTION 13***
    1 = yes, LEFT only ****please COMPLETE Column A in the table below****
    2 = yes, RIGHT only ****please COMPLETE Column B in the table below****
    3 = yes, BOTH breasts ****please COMPLETE Columns A & B in the table below****
    9 = uncertain; please explain _____

Information about your aspiration results. Please circle whether the "finding" was benign, malignant, or unknown. If the finding was ***benign****, please circle hyperplasia, atypia, or unknown.*

COLUMN A – LEFT BREAST			***COLUMN B – RIGHT BREAST***		
	Year of aspiration	Finding (please check one)		Year of aspiration	Finding (please check one
Aspiration #1		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Aspiration #1		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Aspiration #2		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Aspiration #2		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Aspiration #3		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Aspiration #3		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Aspiration #4		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Aspiration #4		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain
Aspiration #5		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain	Aspiration #5		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = unknown 2 = malignant (cancer or in situ) 9 = uncertain

If you had more than 5 aspirations, please write the information in question 30.

GENERAL HEALTH STATUS

13. During the last 5 years, would you say that your health in general was:
    1 = excellent 3 = good
    2 = very good 4 = poor

14. Have you ever had any cancer other than breast cancer?
    0 = no
    1 = yes → Primary site 1: _____ Age at diagnosis ___
    (primary site is where the cancer first occurred, e.g. skin, colon, ovary)
    Primary site 2: _____ Age at diagnosis ___
    Primary site 3: _____ Age at diagnosis ___
    9 = uncertain; please explain _____

15. Have you ever taken medication to prevent pregnancy? (do NOT include barrier methods such as condoms or diaphragms)
    0 = no, never → ***SKIP TO QUESTION 16***
    1 = yes ****please COMPLETE the following table for the medication(s)****
    9 = uncertain; please explain _____

    Please answer for medication(s) you have taken to prevent pregnancy. For medications you have NEVER TAKEN, please leave blank.

Medications to Prevent Pregnancy:	**Total years taken**	**Total months taken**
BIRTH CONTROL PILLS 1 = not now → Year first taken _____ Year last taken _____ 2 = now → Year first taken _____ ☐ Check if not taken continuously		
DEPO PROVERA (injections) 1 = not now → Year first taken _____ Year last taken _____ 2 = now → Year first taken _____ ☐ Check if not taken continuously		
NORPLANT (implants) 1 = not now → Year first taken _____ Year last taken _____ 2 = now → Year first taken _____ ☐ Check if not taken continuously		
PATCH 1 = not now → Year first taken _____ Year last taken _____ 2 = now → Year first taken _____ ☐ Check if not taken continuously		
OTHER, specify: _____ 1 = not now → Year first taken _____ Year last taken _____ 2 = now → Year first taken _____ ☐ Check if not taken continuously		

16. Have you ever taken medications (fertility drugs) to increase your chances of having a child?

0 = no, never 1 = yes (***COMPLETE table below***) ↓ 9 = uncertain

Name of medication	Year first taken	Total years taken	Total months taken

17. Have you ever taken female hormones for menopause?

0 = no, never 1 = yes (***COMPLETE table below***) ↓ 8 = not applicable, premenopausal

Name of medication	Year first taken	Total years taken	Total months taken

18. Have you ever taken Tamoxifen or Raloxifene?

0 = no, never 1 = yes (***COMPLETE table below***) ↓ 9 = uncertain

	Year first taken	Total years taken	Total months taken
Tamoxifen			
Raloxifene			

19. Have you ever taken other medications to prevent breast cancer?

0 = no, never 1 = yes (***COMPLETE table below***) ↓ 9 = uncertain

Name of medication	Year first taken	Total years taken	Total months taken

FAMILY HISTORY

*Please answer the following questions only for your **blood** relatives (living or deceased)*

20. Did your **mother** ever have breast cancer?
    0 = no
    1 = yes → Age at diagnosis _____
    9 = don't know

21a. Do you or did you have any **sisters**?
    0 = no → ***SKIP TO QUESTION 22a***
    1 = yes → How many? _____

    21b. How many of your **sisters** ever had breast cancer? _____ or *don't know*

    21c. For each **sister(s)** who ever had breast cancer, how old was she when it was first diagnosed?

    #1 _____ #2 _____ #3 _____ #4 _____ #5 _____ or *don't know*

22a. Do you or did you have any **daughters**?
    0 = no → ***SKIP TO QUESTION 23***
    1 = yes → How many? _____

    22b. How many of your **daughters** ever had breast cancer? _____ or *don't know*

    22c. For each **daughter(s)** who ever had breast cancer, how old was she when it was first diagnosed?

    #1 _____ #2 _____ #3 _____ #4 _____ #5 _____ or *don't know*

23. Did your **mother's mother** ever have breast cancer?
    0 = no
    1 = yes → Age at diagnosis _____
    9 = don't know

24a. How many **sisters** does (did) your **mother** have? _____ or *don't know*
    (If none, ***SKIP TO QUESTION 25***)

    24b. How many of your **mother's sisters** ever had breast cancer? _____ or ***don't know***

    24c. For each of your **mother's sister(s)** who ever had breast cancer, how old was she when it was first diagnosed?

    #1 _____ #2 _____ #3 _____ #4 _____ #5 _____ or *don't know*

25. Did your **father's mother** ever have breast cancer?
    0 = no
    1 = yes; Age at diagnosis _____
    9 = don't know

26a. How many **sisters** does (did) your **father** have? _____ or *don't know*
(If none, ***SKIP TO QUESTION 27***)

26b. How many of your **father's sisters** ever had breast cancer? _____ or *don't know*

26c. For each of your **father's sister(s)** who ever had breast cancer, how old was she when it was first diagnosed?

#1 _____ #2 _____ #3 _____ #4 _____ #5 _____ or *don't know*

MENSTRUAL AND PREGANCY HISTORY

27. At what age did you start menstruating? _____

28. Are you still having periods?
    1 = yes
    2 = yes, but pregnant, postpartum, or breastfeeding now
    3 = yes, but infrequently, probably perimenopausal
    4 = yes, but due to hormone replacement therapy
    5 = no, went through natural menopause → Age of last period ____
    6 = no, went through natural menopause and later had hysterectomy → Age of last period ____
    7 = no, had a hysterectomy with womb and **one** ovary removed → Age of last period ____
    8 = no, had hysterectomy with womb and **both** ovaries removed → Age of last period ____
    9 = no, had hysterectomy with only womb removed → Age of last period ____
    10 = no, had a hysterectomy, type unknown → Age of last period ____
    11 = no, due to chemo therapy or radiation treatment → Age of last period ____
    12 = other, please specify: _____

29. Have you ever been pregnant or are you pregnant now?
0 = no → ***SKIP TO QUESTION 30***
1 = yes ****please COMPLETE the table below****
2 = currently pregnant ****please COMPLETE the table below for previous pregnancies ****

Pregnancy information:

Pregnancy Number	Outcome (please circle one)	Year Pregnancy Ended	Number of Months the Pregnancy Lasted	Total Number of Months You Nursed (if live born infant)
1st	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
2nd	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
3rd	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
4th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
5th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
6th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY

7th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
8th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
9th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY
10th	1 = live birth 2 = miscarriage 3 = still birth 4 = other,specify _____ 9 = uncertain	_____ Year	_____ Total months	_____ Months breastfed ☐ Check if did not breastfeed, FORMULA ONLY

30. Is there anything else that you would like to tell us?

End of Questionnaire – Thank you very much for your help in this study

Deleted: IF YOU HAVE EVER HAD BREAST CANCER, BREAST SURGERY, A BREAST BIOPSY, OR A FINE NEEDLE ASPIRATION, PLEASE COMPLETE AND SIGN THE PATHOLOGY RELEASE FORM FOUND ON THE LAST PAGE OF THIS QUESTIONNAIRE. ¶

¶

Page Break

Sartorius Follow-Up Study¶

Release Form¶

¶

IF YOU HAVE EVER HAD BREAST CANCER, BREAST SURGERY, A BREAST BIOPSY, OR A FINE NEEDLE ASPIRATION, PLEASE COMPLETE AND SIGN THIS PAGE.

¶

THANK YOU VERY MUCH FOR YOUR COOPERATION.¶

¶

Your name: _____¶

First Middle Last¶

¶

If you had ***breast cancer*** (including *in situ*) where was it diagnosed? (If you've had more than one breast cancer, please refer to the first one).¶

¶

Hospital or clinic: _____¶

¶

Address: _____¶

¶

Telephone: (_____) _____ - _____¶

¶

For other breast procedures performed at different locations or by physicians other than Dr. Sartorius, ***please CIRCLE procedure type performed and provide pertinent information below:***¶

¶

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy ¶

¶

Date: ___/___/___¶

month / day / year¶

¶

Name of doctor: _____¶

¶

Hospital or clinic: _____¶

¶

Address: _____¶

¶

Telephone: (_____) _____ - _____¶

Area code ¶

¶

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy ¶ ... [1]

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IF YOU HAVE EVER HAD BREAST CANCER, BREAST SURGERY, A BREAST BIOPSY, OR A FINE NEEDLE ASPIRATION, PLEASE COMPLETE AND SIGN THE PATHOLOGY RELEASE FORM FOUND ON THE LAST PAGE OF THIS QUESTIONNAIRE.

Page Break

Sartorius Follow-Up Study

Release Form

IF YOU HAVE EVER HAD BREAST CANCER, BREAST SURGERY, A BREAST BIOPSY, OR A FINE NEEDLE ASPIRATION, PLEASE COMPLETE AND SIGN THIS PAGE.
THANK YOU VERY MUCH FOR YOUR COOPERATION.

Your name: _____

First ***Middle*** ***Last***

If you had ***breast cancer*** (including *in situ*) where was it diagnosed? (If you've had more than one breast cancer, please refer to the first one).

Hospital or clinic: _____

Address: _____

Telephone: (___ ___) ___ ___ - ___ ___ ___ ___

For other breast procedures performed at different locations or by physicians other than Dr. Sartorius, ***please CIRCLE procedure type performed and provide pertinent information below:***

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy

Date: ___/___/___
month / day / year

Name of doctor: _____

Hospital or clinic: _____

Address: _____

Telephone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Area code

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy

Date: ___/___/___

month / day / year

Name of doctor: _____

Hospital or clinic: _____

Address: _____

Telephone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Area code

Please see back for additional procedures.

The Department of Physiologic Nursing at University of California, San Francisco, has my permission to obtain tissue samples and medical information concerning my breast cancer, fine needle aspiration (FNA), breast biopsy, and/or mastectomy occurring on the dates given above.

Signed:

_____

Today's Date:

_____

Additional breast procedures:

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy

Date: ____/____/____
month / day / year

Name of doctor: _____

Hospital or clinic: _____

Address: _____

Telephone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Area code

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy

Date: ____/____/____
month / day / year

Name of doctor: _____

Hospital or clinic: _____

Address: _____

Telephone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Area code

Fine Needle Aspiration (FNA) / Breast Biopsy / Mastectomy / Lumpectomy

Date: ____/____/____
month / day / year

Name of doctor: _____

Hospital or clinic: _____

Address: _____

Telephone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Area code

The Department of Physiologic Nursing at University of California, San Francisco, has my permission to obtain tissue samples and medical information concerning my breast cancer, fine needle aspiration (FNA), breast biopsy, and/or mastectomy occurring on the dates given above.

Signed: _____

Today's Date: _____

Please do NOT put your name on this form ID#

SARTORIUS FOLLOW UP STUDY
University of California, San Francisco
Department of Physiological Nursing

Please complete this questionnaire concerning your mother/wife/sister/daughter/friend by **circling or filling in** the appropriate answers regarding her breast cancer experience.

1. Today's date: _____/_____/_____
   month / day / year

BREAST CONDITIONS AND STATUS

2. Did she ever have breast cancer?
   0 = no
   1 = yes, right breast only → Year first found_____ or *don't know*
   2 = yes, left breast only →Year first found _____ or *don't know*
   3 = yes, both breasts →Year first found _____ or *don't know*
   9 = uncertain; please explain _____

2a. How was the first breast cancer found, if more than one? (Circle all that apply)
   1 = self exam
   2 = clinical breast exam
   3 = mammogram
   4 = ultrasound
   5 = biopsy
   6 = other, please specify: _____
   9 = uncertain; please explain _____

3. Did she ever have a mastectomy (removal of a breast)?
   0 = no, never
   1 = yes, right breast only → Year procedure was done _____
   2 = yes, left breast only → Year procedure was done _____
   3 = yes, both breasts → Year procedure was done _____
   9 = uncertain; please explain _____

4. Did she ever have a mammogram (x-ray of a breast)?
   0 = no, never
   1 = yes → Year of first mammogram ____ / Year of most recent mammogram ____
   9 = uncertain; please explain _____

5. Did she ever have a breast biopsy?
   0 = no, never → skip to question 11
   1 = yes, right only *please complete the following table*
   2 = yes, left only *please complete the following table*

3 = yes, both breasts *please complete the following table*
9 = uncertain; please explain _____

5a. Information about her biopsy results. Please circle (if information is available) whether the finding was either benign, malignant or unknown. If the finding was benign, please circle whether it was hyperplasia, atypia or don't know.

Left breast	Year of biopsy	Finding (please circle benign, malignant or uncertain)	**Right breast**	Year of biopsy	Finding (please circle one)
Biopsy #1		1 = benign ↓ if yes, circle 1,2 or 3 1 = hyperplasia 2 = atypia 3 = don't know2 = malignant (cancer) 9 = uncertain	Biopsy #1		1 = benign ↓ if yes, circle 1, 2 or 3 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain
Biopsy #2		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain	Biopsy #2		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain
Biopsy #3		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain	Biopsy #3		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 =uncertain
Biopsy #4		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain	Biopsy #4		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain
Biopsy #5		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain	Biopsy #5		1 = benign ↓ 1 = hyperplasia 2 = atypia 3 = don't know 2 = malignant (cancer) 9 = uncertain

6. What was the cause of death? _____

End of Questionnaire – Thank you

EXPLORING EARLY DETECTION METHODS: USING THE INTRADUCTAL APPROACH TO PREDICT BREAST CANCER RISK

Kimberly Baltzell , RN, PhD(c); Jennette Sison ,MPH; Margaret Wrensch , PhD

ABSTRACT

Current methods of breast cancer detection are limited, particularly for women under 50. Looking at atypical cellular cytology from breast fluids may provide more accurate biologic markers from which *to assess individual risk. The purpose of this study is to replicate* the findings of the only other prospective study of breast cancer in women with known cytologic findings from nipple aspiration. This study showed a significant relationship between the presence of atypical hyperplasia and increased risk of breast cancer development.

THEORETICAL/SCIENTIFIC FRAMEWORK: *Current theories of* breast carcinogenesis and malignant transformation support the notion of breast cells progressing on a continuum from normal to atypical to malignant.

METHODS:

Study Design The study will be a historic prospective cohort study. A 15-to 30-year follow-up study *will be conducted to determine breast* cancer incidence among women with known breast fluid cytologic findings. Each subject will be classified into one of five cytological categories. Univariate survival analysis will be used to compare the categoric predictor variables with the breast cancer absence or presence of/death from breast cancer. Proportional hazards regression will be used to complete the analysis.

Study Population Participants to be included in this follow-up are women who were patients of Dr. Otto Sartorius in his Santa Barbara clinic between 1970 and 1990. Dr. Sartorius was a pioneer in breast fluid studies. The total number of patient records available for analysis is 3413.

Data Collection Procedures Follow-up methods will be used which are similar to methods used in the Wrensch et al (2001) study. These methods include 1) direct contact, 2) linkage with the Surveillance, Epidemiology, and End Results Program (SEER) tumor registry data at the California Cancer Registries (CCR), 3) *linkage with the Northern California* Cancer Center (NCCC), 4) linkage with a national tumor registry, 5) linkage with state of California mortality data and 6) linkage with the National Death Index (NDI).

DATA ANALYSIS:

The study will explore whether or not the presence of DH and ADH are *significant in predicting breast cancer development while* controlling for age, age at menarche, age at first pregnancy and family history of breast cancer. Proportional hazards regression will be used to determine if the unique contribution of DH and ADH to the hazard ratio is significant while controlling for the variables defined above.

This work is supported by the Department of Defense (#DAMD17-02-1-0221)

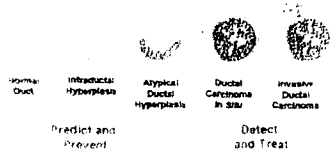
BACKGROUND

Breast cancer is the leading cause of death for women between 40 and 55 years of age and the second leading cause of death for women over 55. Early diagnosis is believed to be a key to minimizing mortality; thus, techniques to identify high-risk women are essential. Breast self-examination (BSE) is under scrutiny for its' questionable value in improving mortality rates in women who have detected their tumor using this method. Mammography is now being reanalyzed for overall effectiveness in improving mortality rates for breast cancer. Identifying women who are at high risk for developing breast cancer is extremely difficult, as only 5-10% of breast tumor appear to have a genetic link. Since 95% of breast tumors begin in the lining of the milk ducts of the breast, it is logical to explore *these ducts as a means of identifying abnormal cells that may eventually progress into tumors.*

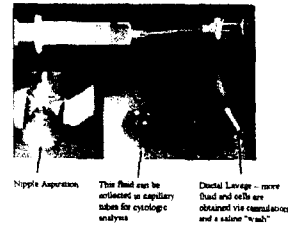
Previous studies evaluating breast fluids have found a significant difference between women with abnormal cells in their fluids and women with normal cells; women with abnormal findings in their fluids developed breast cancer at a greater rate.

Nipple aspiration, ductography, and lavage are methods for obtaining fluid from breasts of women who are neither pregnant nor lactating. Breast epithelial cells in this fluid can be classified *as either normal or as showing* various abnormalities including hyperplasia, atypical hyperplasia, and cancer. As early as 1977, Otto Sartorius, MD, a pioneer in nipple aspirate techniques found evidence of the congruence between cytology in breast fluids and subsequent pathology from biopsies of breast tissue. For instance, in a study of 1706 women attending a breast clinic, biopsies found small carcinomas in 18 of 27 women (66%) with fluids classified as suspected carcinomas. Also of note, of 67 carcinomas detected in that study, 7 were diagnosed solely by cytologic study of aspirated breast fluids (palpation and mammography were negative).

The goal: Identify women at highest risk so they can be targeted for a proactive risk management strategy



Steps in nipple aspiration and ductal lavage (reprinted by permission from Susan Love MD).



STUDY POPULATION

Participants to be included in this follow-up are women who were breast clinic patients, some of whom were included in a previous breast fluid study conducted by Dr. Otto Sartorius, in *the Santa Barbara Area between 1970 and 1990. The total of* patients available for follow-up is 3413 women. A data abstracting team has recently completed abstracting detailed information to be used as baseline information from all 3413 patient records, including demographic information, breast health, and cytology results. I propose to follow these women to determine breast cancer incidence through 2004.

Breast fluids were collected from these women using various methods. A follow-up study after 15-30 years will give us invaluable information, both by determining breast cancer incidence among these women with known breast fluid cytologic findings who have not yet been followed and by correlating findings from different breast fluid collection methods (nipple aspiration, ductography, lavage). There are no other large cohorts of women with known breast fluid findings with which to replicate the original findings in San Francisco other than those from the Santa Barbara Breast Diagnostic Clinic.

Breast Epithelial Cell Extraction Methods – Pros and Cons

Method	Description	Pros	Cons
[illegible]	Use of nipple suction [illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]
Ductal Lavage	Use of microcatheter to cannulate ductal orifices "wash" ductal cells and collection container for analysis	-done without an anesthetic -yields large number of cells for analysis	-more invasive than nipple aspiration -low risk of infection or injury to the breast -not all ducts are sampled
Fine-needle Breast Needle Aspiration	Use of small needle to remove cells from the breast tissue for analysis	-do not need intact ductal system to obtain cells for analysis	-invasive procedure -accuracy of readings depends on experience of professional performing procedure

SARTORIUS COHORT DEMOGRAPHIC DATA

Age* in year of first contact:	N
Under 20	63
20-34	860
35-49	1262
50-64	796
65 & older	428
No data	4
Ethnicity:	
White	493
African-American	12
Amer-Indian	1
Asian/Pacific Islander	0
Hispanic	38
No Data	2863
Age at Menarche: (ages in years)	
<10	127
10-12	945
13-14	1388
>14	377
No data	571
Outliers	4
Age at First Pregnancy: (ages in years)	
8-15	76
16-20	[illegible]
21-25	940
26-30	184
31-35	46
36-43	50
Nulliparous	1011
No data	106
NAF Collection Procedures	# of Patients/not Proc.
Ductograms	476/610
Fine Needle Aspiration	unknown/3373
Lavage	unknown/608
Nipple Asprate	unknown/629**
Patients with Malignancy on First Contact	464
TOTAL Number of Patients	3413

*Age range 10-90 years
**Includes unsuccessful procedures (e.g. unable to cannulate, no fluid obtained)

OBJECTIVES & HYPOTHESIS

Because of the limitations of current methods, new breast cancer detection methods must be developed. An ideal detection method would be one that is not prohibitively expensive and provides true "early detection"- detection of the changes in cells that precede actual invasive cancer rather than identifying cancer after it has had the chance to spread throughout the body. Such a method should also have the capability of providing an accurate determination of a woman's individual breast cancer risk. The possibility of developing this type of early detection is supported by work in previous studies that have documented a link between *abnormal cell cytology in breast fluid (e.g., nipple aspirate fluid) and the* subsequent development of breast cancer. For this study which will be used for my doctoral dissertation, I will look at a group of 3413 women from whom breast fluids were obtained via nipple aspiration, ductography, or ductal lavage in the period between 1970 and 1990 to determine (a) how many women from this group of women have developed breast cancer and (b) the relationship of breast cancer development to cytology of breast fluids obtained up to 30 years ago.

My hypothesis based on previous findings is that women with proliferative cytologic findings will be 2.0 to 5.0 times as likely to have developed breast cancer as women with *normal cytology or who did not* yield fluid. Also, based on previous research, I expect that breast fluid cytology findings will enhance the predictive value of other risk factors for breast cancer including prior breast biopsy and positive family history of breast cancer.

POTENTIAL OUTCOMES and RELEVANCE OF RESEARCH

This proposal explicitly addresses three different priority issues specific to breast cancer: (a) to find methods to improve earlier detection of breast cancer, (b) to develop models that help identify women at highest risk of developing breast cancer, and (c) to prepare qualified medical / nursing personnel for a career in breast cancer research. The result of this proposed study will be twofold: (a) it will provide me with knowledge and experience regarding the early detection of breast cancer and (b) it will provide information useful for identifying women at highest risk of breast cancer who could be recruited into studies aimed at preventing breast cancer. This study has immediate relevance to early detection of breast cancer and to identification and careful characterization of women at high risk of breast cancer. A team approach using experienced professionals from nursing, biostatistics, and epidemiology will create a training opportunity aimed at bolstering my preparation for a career as a clinical nurse breast cancer researcher.

Breast Carcinogenesis—Can the Examination of Ductal Fluid Enhance Our Understanding?

Kimberly Baltzell, RN, PhD(c), Suzanne E. Eder, NP, RN, and Margaret Wrensch, MPH, PhD

Purpose/Objectives: To explore current breast carcinogenesis theories and the possibility of examining breast epithelial cells to confirm steps in the carcinogenic process and the relationship between intraductal sampling techniques and their role in enhanced risk prediction.

Data Sources: Published articles, textbooks, and conference proceedings.

Data Synthesis: Examining breast epithelial cells may provide insight into the carcinogenic process while it is occurring. Methods of extracting breast epithelial cells include nipple aspiration, ductal lavage, and periareolar fine-needle aspiration.

Conclusions: Nipple aspiration, ductal lavage, and periareolar fine-needle aspiration are viable means of examining possible precursors to breast tumors. Differentiating between true precursors and benign changes is an important step in breast cancer risk assessment.

Implications for Nursing: Nipple aspiration and ductal lavage may be performed in an outpatient setting. RNs and advanced practice nurses may perform these procedures and discuss results with patients.

Key Points . . .

- Many breast carcinogenic theories support the notion of a cellular continuum from normal epithelium through multiple proliferative stages to malignancy.
- Examining breast epithelial cells over time to determine when premalignant changes occur may lead to enhanced risk prediction.
- Obtaining breast epithelial cells via nipple aspiration, ductal lavage, or periareolar fine-needle aspiration may be a less invasive way to acquire information on breast cancer risk than currently achieved by breast biopsy.

An understanding of normal cellular transformation to malignancy is not defined clearly in the study of breast cancer. Deciphering the breast cancer pathophysiologic pathway is necessary for the design of effective cancer prevention strategies (Miller, Bates, & Nabell, 2002). Recent studies showing a significant association between proliferative breast cells and increased risk of breast cancer development highlight the importance of clarifying precursors to disease development (Fabian & Kimler, 2001; Wrensch et al., 2001). Studzinski and Harrison (2002) wrote that precise breast cancer diagnosis, monitoring, and treatment require understanding the control of cell growth, which may lead to the ultimate goal—prevention. Studying the progression from normal cell growth patterns to malignancy has been difficult because of the populations on whom most research has been performed. These populations typically include patients with advanced or metastatic disease. These studies may be limited in their usefulness because events surrounding carcinogenesis already have taken place (Briand & Lykkesfeldt, 2001). Researchers generally agree that carcinogenesis is a result of a combination of inherited susceptibility (germline mutations) and acquired genetic changes (somatic mutations), possibly involving more than 200 genes (Miller et al.; Studzinski & Harrison). This article will discuss the current theories of breast carcinogenesis, emphasizing the progression of normal cells through malignant transformation. Carcinogenesis theory lends support to the idea of using breast epithelial cells to analyze possible precursors to malignancy, leading to enhanced breast cancer risk-prediction models. Types of intraductal sampling techniques will be reviewed, as well as the correlation between tissue cytology and intraductal cytology.

Kimberly Baltzell, RN, PhD(c), is a doctoral candidate in the Department of Physiologic Nursing at the University of California, San Francisco (UCSF), Suzanne E. Eder, NP, RN, is a nurse practitioner at the UCSF Breast Care Center, and Margaret Wrensch, MPH, PhD, is a professor in the Departments of Neurological Surgery and Epidemiology/Biostatistics at UCSF. *(Submitted December 2003. Accepted for publication September 3, 2004.)* *(Mention of specific products and opinions related to those products do not indicate or imply endorsement by the* Oncology Nursing Forum *or the Oncology Nursing Society.)*

Digital Object Identifier: 10.1188/05.ONF.33-39

Carcinogenesis Theory Overview

Development of Breast Cells

Breast cells begin to complete their growth during puberty. Prior to that time, the mammary gland consists of a fat pad with a primary duct and several ductal branches (Miller et al., 2002). With the onset of menarche, rapid growth occurs, regulated by estradiol and progesterone. The cyclic nature of estrogen exposure continues to act on the breast tissue, yet ductal development stops after puberty is completed.

Although the formation of ducts is over, the duct end buds continue interchanging rounds of growth and cessation in response to hormonal changes produced by the menstrual cycle (Miller et al., 2002). This balance of proliferation and apoptosis (cell death) keeps the breast epithelium in check, and imbalance in this system is the basis of many carcinogenesis theories. The protective effect of full-term, early pregnancy is linked to its association with ductal differentiation, leaving breast cells less vulnerable to these cyclic events that may lead to cancer development.

Estrogen is thought to play a key role in the development of normal breast cells, as well as the development of breast cancer cells (Allred, Mohsin, & Fuqua, 2001). Estrogen is responsible for the elongation of breast ducts and thickening of the epithelium that occurs in puberty (Rosen, 2001). Differentiation of the lobuloalveolar units occurs during puberty, with insulin, progesterone, and growth hormone contributing to the process (McCarty & Tucker, 1992; Rosen). These changes continue through menstrual cycles, pregnancy, lactation, and menopause.

Carcinogenesis Theories

Carcinogenesis is described as a multistage process whereby normal cell proliferation continues unchecked because of aberrant genetic or chromosomal alterations, leading to invasive and metastatic growth (Briand & Lykkesfeldt, 2001).

Cancer of the breast generally is divided into two etiologic origin groups. The first group is cancer that is deemed to arise from strong hereditary sources, primarily a mutation of either the *BRCA1* or *BRCA2* gene (Miller et al., 2002). These germline mutations are believed to be responsible for about 5%–10% of all breast cancers and 65% of all inherited breast cancers. The second group of breast cancers, the remaining 90%, is defined as sporadic and nonfamilial. The processes for both types of cancers, however, seem to be a combination of genetic susceptibility and epigenetic factors (Briand & Lykkesfeldt, 2001). Epigenetic factors are defined as altered expression of genes, although base pairs remain unchanged (Tannock & Hill, 1998). Epigenetics may hold great promise for future interventions, given that epigenetic alterations are reversible and mutations are not.

What is known about carcinogenic pathways? Five individual steps necessary for malignant transformation have been proposed (Hahn & Weinberg, 2002). The steps are independence from mitogenic stimulation, evasion of apoptosis, immortalization, resistance to exogenous growth-inhibitory signals, and angiogenesis.

Mitogenic stimulation independence may occur as a result of the mutation of an oncogene (e.g., ras, HER2-neu), in essence turning on a cell's ability to override its own growth control checks. Cancer cells do not depend on external signals to make a commitment to proliferate (Hahn & Weinberg, 2002). A breast cancer oncogene of interest is HER2-neu. Mutations of these genes may occur by base substitutions, translocation, amplification, or viral insertions. Whatever the method of mutation or activation employed, the affected cell takes on an enhanced capacity for growth. HER2-neu is an oncogene that frequently is overexpressed in tumors (Miller et al., 2002). Tumors with an abundance of this oncogene often have poorer responses to chemotherapy; however, this is an exciting area of exploration for new treatment modalities.

The evasion of apoptosis might occur as a result of a mutated tumor suppressor gene (e.g., p53) inhibiting the back-up system in place for both cell overgrowth and damaged cell surveillance and repair. Mutated p53 is present in about 30%–40% of human cancers (Dickson & Lippmann, 2000). It is the most frequently studied tumor suppressor gene, which, under normal circumstances, functions as an apoptosis inducer or inhibitor of cell overgrowth. Mutated p53 interferes with normal p53, and researchers have speculated that restoring normal p53 may inhibit cancer growth (Yin, Tainsky, Bischoff, Strong, & Wahl, 1992).

Immortalization results from damage to telomeres (the chromosomal end caps), allowing cells to maintain their proliferative potential indefinitely. Even in the presence of proper nutrients and space, normal cells stop dividing as the telomeres shorten and no longer can stabilize chromosomes. A malignant cell, in contrast, maintains its proliferative potential indefinitely. Molecular mechanisms that inhibit this cell senescence are unclear (Tannock & Hill, 1998).

Resistance to exogenous growth-inhibitory signals works in tandem with one of the other behaviors of cancer cells, independent mitogenic stimulation, allowing cells to proliferate unchecked. All interrupted pathways lead to the hallmarks of malignancy: an increase in cell proliferation and lack of cell death. Finally, the ability of a cell to create additional blood flow appears to be a trait of cancer cells. Circulatory access is believed to be necessary for a tumor to grow larger than two centimeters.

Hormones play a major role in the development of breast cancer. Henderson, Pike, Bernstein, and Ross (1996) wrote that the role of hormones involves their effects on breast cell proliferation and that this increased cell division is vital for the genesis of human cancer. They also cited the activation of oncogenes and mutation of tumor-suppressor genes as necessary for the development of a malignant phenotype. This progression is illustrated in Figure 1.

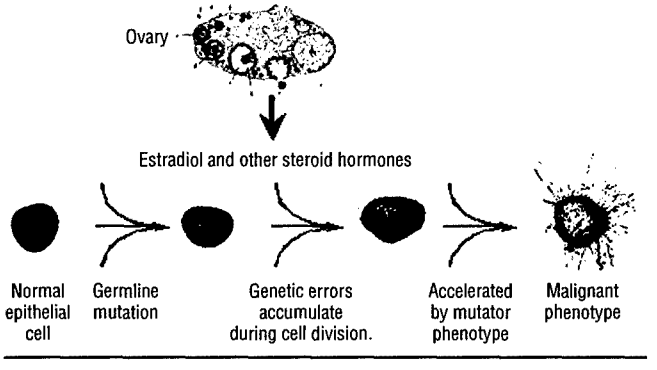


Figure 1. Progression to Malignant Phenotype

Note. Based on information from Henderson et al., 1996.

Knudson (1971) inspired many carcinogenesis models based on his theory of a multistep process involving an initial "hit" of one of the tumor-suppressor gene alleles, inactivating it, resulting in homozygosity of the chromosome. In addition, cell division is required for all processes leading to breast cancer development. This theory supports a cellular continuum of normal cell appearance through an abnormal proliferative phase, followed by the progression to a malignancy.

Other studies have debated the hypothesis that cancer arises from mutations. Prehn (1994) wrote that mutations may have limited biologic significance. Cancer is hypothesized to give rise to mutations, rather than mutations giving rise to cancer. This theory is based on the epigenetic events surrounding breast cancer development; however, progression from a normal cellular state through abnormalities into malignancy is supported.

Vineis (2003) proposed a Darwinian approach to carcinogenesis whereby epigenetic events influence a cell's decision to progress to malignancy. The two phases are genetic change followed by selective advantage. The resistance of cells to events such as apoptosis allows for survival of the fittest, allowing mutated cells to adapt more readily to specific environmental niches better than normal cells. Vineis used this hypothesis to explain the difference in international rates of breast cancer because genetic differences account for only a small portion of the variation. Changes in environment as well as the presence of "selective advantage" combine to create cancer rates for specific populations. Willet, Rockhill, Hankinson, Hunter, and Colditz (2000) attributed the increase in breast cancer incidence in women who migrated from low-risk countries (primarily Asian) to high-risk countries (primarily Northern European) to the length of time spent in the high-risk country and adoption of the destination country's lifestyle.

Briand and Lykkesfeldt (2001) reviewed a decade of work on a human breast epithelial cell line, HMT-3522, to formulate an epigenetic model for breast carcinogenesis. They cautioned that following breast cancer events in advanced cases does not illuminate events related to how carcinogenesis actually begins. They believed that cell culture is an appropriate medium for exploring the events that lead to malignant transformation. The study's hypothesis suggested that mutation is a necessary step in the carcinogenesis process; however, epigenetic events influence which cells progress to cancer.

The primary assumption made in the study of breast carcinogenesis is the notion of cells progressing on a continuum. Although which cells will progress to a malignant state from a proliferative state (hyperplasia or atypia) is unknown, recent studies showing an increased risk of breast cancer development in women with proliferative findings have suggested a relationship (Wrensch et al., 2001). The ability to invade surrounding breast tissue and metastasize is present in 20%–50% of breast precancers (O'Shaughnessy, 2000). If hyperplasia and atypical hyperplasia are the result of the first several steps in the process outlined by Hahn and Weinberg (2002), identifying these cellular changes prior to circulatory access and commitment to metastasis is critical. The theory of malignant transformation using cell culture supports the concept of malignant conversion (Martin, 1996). By recognizing the progression of abnormal cell development as a continuum, some borderlines have been created between benign states and malignancies. Page and Rogers (1992) disputed the idea of categorizing cells as either benign or malignant. All tumor cells are believed to have sprung from a single cell, and tumor progression is a phenomenon that concludes that benign tumors often evolve into malignancies (Martin). A malignant phenotype arises from the cell population with the most rapid and favored growth pattern. The earlier discussion supports the idea of benign cells revealing changes that may be indicative of a progression to cancer. Perhaps the analysis of breast epithelial cells will illuminate important precursors to breast cancer. Evidence of intraductal and atypical hyperplasia in epithelial cells may allow for prediction and prevention of breast cancer, whereas advanced progression to invasive cancer requires more aggressive vigilance and treatment (see Figure 2.).

Evaluating Breast Cancer Risk

The most commonly used models for evaluating breast cancer risk are the Gail model, the Claus model, and BRCAPRO (developed by statisticians at the Duke University Institute for Statistics and Decision Sciences). Each model was designed from a different population, and, because the models are not used uniformly in clinical practice, the accuracy of the results is a function of healthcare providers' knowledge.

The Gail model uses age, age at menarche, number of prior breast biopsies, age at first live birth, and number of first-degree relatives affected by breast cancer to assess risk. Absolute risk is calculated for five years from the time of assessment and lifetime risk up to age 90 (Gail et al., 1989). The model is most appropriate for evaluating risk in women with limited family history of breast cancer. The Gail model uses limited family history of breast cancer and tends to overestimate risk in young women (Kelly, 2000).

Another breast cancer risk assessment model was developed by Claus, Risch, and Thompson (1993). The model addressed several of the alleged shortcomings of the Gail model by incorporating more extensive family history into the analysis. In addition, the Claus model integrates age at diagnosis of breast cancer into its calculations. This information has become more important since the discovery of *BRCA1* and *BRCA2* mutations, allowing healthcare professionals to consider the possibility of recommending genetic testing. This model is most helpful in determining risk for women with a strong family history of breast cancer. The nonfamily history information included in the Gail model is not considered in the Claus calculations.

Goal: Identify women at highest risk so they can be targeted for a proactive risk management strategy.

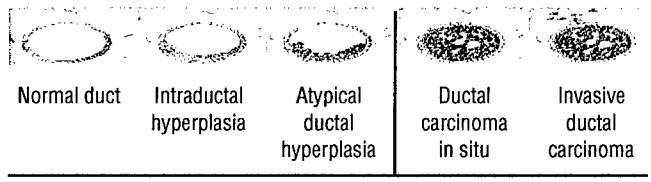


Figure 2. Cellular Progression From Normal Duct Epithelium to Carcinoma

Note. Image courtesy of Cytyc Corporation and affiliates. Used with permission.

Computer programs also have been designed to assess women's risk of a *BRCA1* or *BRCA2* mutation. The BRCAPRO program is considered to be the most comprehensive estimate of genetic mutation risk and has been compared favorably against the assessment of experienced risk counselors (Euhus, Smith, et al., 2002).

Although each of the models is useful in specific populations, no tool completely captures the many factors believed to contribute to a woman's risk of developing breast cancer. Viewing cells directly from the breast duct epithelium would allow the addition of biologic information to models of risk assessment. Cells can be obtained through nipple aspiration, ductal lavage, and periareolar fine-needle aspiration (FNA).

Obtaining Epithelial Cells to Evaluate the Carcinogenic Process

The ability to study breast epithelial cells for precancerous changes is necessary to evaluate where in the carcinogenic process intervention is most effective. Studies that have found a strong association between the presence of hyperplasia and atypical hyperplasia and future breast cancer development give this exploration credibility (Fabian et al., 2000; Wrensch et al., 2001). Tissue biopsy is an unrealistic screening tool in large populations of women. Other less invasive methods of obtaining breast epithelial cells include nipple aspiration, ductal lavage, and periareolar FNA. Although no specific screening guidelines exist at present, all results obtained from these methods are interpreted in the context of a breast cancer risk assessment. Appropriate candidates for epithelial cell study include women with a family history of breast cancer, a known genetic mutation such as *BRCA1* or *BRCA2*, or a prior history of breast cancer (to assess the contralateral breast). Additionally, these women should be asymptomatic with a normal breast examination and screening mammogram.

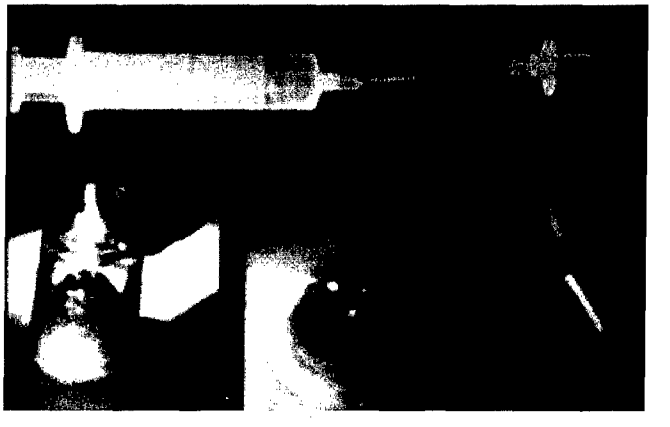
Nipple Aspiration

Obtaining breast epithelial cells through a simple suction technique is known as nipple aspiration. This technique was pioneered by George Papanicolaou, MD, based on cytopathologic evaluation of cervical specimens and their relationship to cervical cancer (Papanicolaou, Holmquist, Bader, & Falk, 1958). Studies have shown varying degrees of success in obtaining nipple aspirate fluid (NAF) using aspiration. Sauter et al. (1997) concluded that NAF can be obtained in essentially all eligible subjects. Other studies have reported that nipple aspiration is far inferior to other techniques such as ductal lavage in obtaining an adequate number of cells for evaluation (Dooley et al., 2001). Past studies have obtained NAF from as few as 25% to as many as 95% of study subjects (Rose, Lahti, Laakso, Kettunen, & Wynder, 1986). Wrensch et al. (2001) noted that obtaining fluid depends on the quantity of fluid present, duct and nipple characteristics, subject age, and the skill of the technician collecting the fluid. Wrensch et al. (1990) found that four important factors were positively related to the ability to obtain breast fluid: age up to 35–50 years, earlier age at menarche, non-Asian compared to Asian ethnicity, and history of lactation. Of interest is the finding that women who do not yield fluid may be less likely to develop breast cancer than women who do yield fluid (Wrensch et al., 1992).

Ductal Lavage

Clinically, ductal lavage is used as a risk assessment tool and in the assessment of suspicious nipple discharge. Ductal lavage has its most important clinical application as a risk assessment tool and is best used in a breast cancer prevention program that addresses the broader issues of breast cancer prevention. Ductal lavage is described as a procedure that uses a microcatheter to cannulate identified ductal orifices for the collection of breast epithelial cells for analysis (Dooley et al., 2001) (see Figure 3). The procedure is performed with only topical anesthesia to facilitate cannula insertion. Dooley et al. found that of 507 women tested, a majority (78%) of subjects' samples were adequate for analysis. The study used comparison groups, examining specimen adequacy of ductal lavage versus nipple aspiration. Of the subjects who underwent ductal lavage, a median of 13,500 cells were collected per duct, with 24% of the subjects showing cellular abnormalities ranging from mild atypia to malignancy. The procedure was well tolerated, with most subjects rating the pain on par with mammography. In addition, ductal lavage was 3.5 times more likely to result in a cytologic diagnosis than nipple aspiration ($p < 0.001$). The abundance of cells available from ductal lavage makes it a promising tool to enhance risk assessment. Informed consent is obtained prior to the procedure. When educating a woman about ductal lavage, healthcare providers should discuss the procedure, possible adverse effects, possible results, and their implications.

Ductal lavage has five potential cytologic interpretations: benign, inadequate cellular material for diagnosis, mild atypical cells, marked atypical cells, or malignant. In discussions about the implications of ductal lavage, healthcare providers must explain that ductal lavage is not a screening tool for breast cancer. Ductal lavage is not a substitute for screening tests such as mammography. The false-negative rate of ductal lavage has not been defined. Women should be counseled about the possible results of ductal lavage and their implications. When the result is benign, the woman must be



Nipple aspiration

This fluid can be collected in capillary tubes for cytologic analysis.

Ductal lavage—More fluid and cells are obtained via cannulation and a saline wash.

Figure 3. Steps in Nipple Aspiration and Ductal Lavage

Note. Image courtesy of Susan Love, MD. Used with permission.

counseled that several ducts have not been sampled. A benign result gives information on only the ducts sampled. Follow-up would include ductal lavage performed on a yearly basis for continued risk assessment. The frequency of follow-up ductal lavage remains, however, a study question. It currently is based on the frequency of traditional screening methods used in breast cancer, such as mammography.

Limitations of this method include the possibility of infection, injury to the breast, and technical problems that affect cell collection (e.g., dehydration, cold) (Esserman, Adduci, Chew, & Ljung, 2003). In addition to these limitations, ductal lavage is not yet considered the standard of care in breast cancer prevention. Most insurance companies will not authorize or provide reimbursement for ductal lavage. The current fee for ductal lavage is about $900 per duct. During a ductal lavage, as many as four ducts may be accessed. Patients may receive ductal lavage by participating in study protocols, in which case they are not burdened with providing payment.

Fine-Needle Aspiration

FNA often is recommended for clinical diagnosis of suspicious breast lumps (Hughes, Mansel, & Webster, 2000). This procedure provides highly accurate information (99% accuracy rate) when performed by skilled practitioners and read by experienced cytopathologists (Barrows, Anderson, Lamb, & Dixon, 1986). In addition to providing diagnostic information about breast lumps, periareolar FNA is being explored as a potential methodology for assessing cellular characteristics leading to increased breast cancer risk (Fabian et al., 2000). Fabian et al. suggested that limitations of other methods discussed earlier point to the feasibility of using periareolar FNA to obtain specimens for risk assessment. In their study, which updated results from a cohort of 480 high-risk women (defined as having one of the following major risk factors: family history of breast cancer, prior lymph node-negative breast cancer, or a prior biopsy indicating atypical lobular or ductal hyperplasia or carcinoma in situ), cytologic evidence of atypical hyperplasia was predictive of breast cancer development. The authors cautioned that this procedure is best employed with women who are premenopausal or those who are postmenopausal and receiving hormone replacement therapy (HRT) because of the limitations of periareolar FNA in obtaining adequate specimens in fatty or involuted breast tissue. HRT delays the development of fatty breast tissue, maintaining a breast structure similar to premenopausal breast tissue. Other studies have used periareolar FNA to enhance individual risk assessment (Euhus, Cler, et al., 2002). Using loss of heterozygosity in breast epithelium as the marker of interest, Euhus, Cler, et al. were able to demonstrate that periareolar FNA may be a feasible method for molecular analysis to define subsets of high-risk women. Masood (1999) emphasized the importance of standardizing both the practice and interpretation of periareolar FNA to justify its use in breast cancer studies, paying particular attention to well-established cytomorphologic criteria (see Table 1).

Correlation Between Tissue Cytology and Intraductal Cytology

If any of the methods of extracting breast epithelial cells are to be useful in assessing risk, a strong correlation must be present between findings in tissue biopsy (the current gold standard for analyzing breast cell changes) and less invasive means of obtaining those cells. Because 90% of breast cancers are believed to be of ductal-lobular origin, analyzing cells from the ducts to determine whether any precancerous changes have taken place is logical. King, Chew, Petrakis, and Ernster (1983) assigned strict criteria for evaluating cytomorphologic changes in breast epithelial cells. The most important finding of their study was the significant association between atypical hyperplasia found in epithelial cells in nipple fluid and atypical hyperplasia found in biopsy tissue. The authors also concluded that the relationship between atypical hyperplasia in the two sources was most significant for women with more marked changes. Using epithelial cells from breast fluid was less reliable for women with benign breast disease. In addition, the study was one of the first to compare cytology between nipple fluid and biopsy using morphologic terms applied to tissue biopsy. One study, which evaluated cells from nipple aspiration only, found cytologic and histologic correlation only when ductal carcinoma in situ and extensive nipple involvement were found in the tissue biopsied (Krishnamurthy et al., 2003). This may be a limitation overcome by using one of the other methods outlined earlier, such as ductal lavage or FNA.

Sensitivity and Specificity Issues

To provide meaningful information, methods of obtaining epithelial cells must have acceptable levels of sensitivity and specificity. Sensitivity is defined as the ability of the test to truly determine the presence of a real breast cancer precursor, and specificity is the ability of the test to correctly identify cells that would not lead inevitably to breast cancer (Last, 2001). Sensitivity is the rate of true positives; specificity is the rate of true negatives.

Ductal lavage yields abundant epithelial cells for evaluation (Dooley et al., 2001). Cytologic studies are performed easily on these specimens; however, what to do with the information remains unclear. Recent studies have questioned the sensitivity and specificity of this method, suggesting that it remains a breast cancer detection method best used in clinical trials (Domchek, 2002). Dooley et al. found ductal lavage to be 3.2 times more sensitive in detecting abnormalities in breast cells than nipple aspiration (79 versus 32 breasts) in a study of 507 women. Sensitivity is less of a concerning issue than specificity in ductal lavage. Until breast carcinogenesis theory is elucidated further, what actions to take in response to abnormal findings remains unclear.

Nipple aspiration is less invasive than ductal lavage; however, the number of cells available for study from aspiration is limited. Dooley et al. (2001) compared cellular yield between ductal lavage and nipple aspiration and found a significant difference (13,500 cells versus 120 cells, respectively). Additional studies have found that cytologic evaluation of nipple aspiration is not useful given its low predictive value (Krishnamurthy et al., 2003; Shao & Nguyen, 2001). The authors speculated that if breast cancer was present, the ducts probably were obstructed and cancer cells would not be aspirated. Because the precise precursors to carcinogenesis have not been defined clearly, searching for more accurate tumor markers is recommended as a priority.

FNA is associated with a high rate of accuracy under optimal circumstances (Barrows et al., 1986). A study of 1,158 FNAs concluded that the procedure is sensitive and specific

Table 1. Pros and Cons of Breast Epithelial Cell Extraction Methods

Method	Description	Pros	Cons
Nipple aspiration	Use of simple suction technique employing a handheld device; droplets of nipple fluid are collected via capillary tube for analysis.	• Completely noninvasive • Inexpensive • Can be done by any trained healthcare professional • Can be collected outside the clinical setting	• Ability to collect fluid depends on ability of healthcare professional if woman has secreting ducts. • Fewer cells are available for cytologic diagnosis compared to ductal lavage.
Ductal lavage	Use of microcatheter to cannulate ductal orifices; saline wash removes cells in collection container for analysis.	• Performed with a topical anesthetic only • Yields large number of cells for analysis	• More invasive than nipple aspiration • Low risk of infection or injury to the breast • Not all ducts are sampled.
Periareolar fine-needle aspiration	Use of a small needle to remove cells from the breast tissue for analysis	• Do not need intact ductal system to obtain cells for analysis	• Invasive procedure • Accuracy of readings • Depends on experience of healthcare professional performing procedure

when used to evaluate clinically suspicious breast masses (Ariga et al., 2002). In groups of women divided by age (40 years and younger versus 41 years and older), sensitivity was 99% and 98% and specificity 99% and 97%, respectively. Having established a cytologic and histologic correlation in FNA, its usefulness as a risk assessment tool is being studied (Fabian et al., 2000).

Sensitivity and specificity traditionally have been used as markers to evaluate the accuracy of a diagnostic tool. These evaluation standards are not applied easily to the use of breast epithelial cells as markers of breast cancer risk versus as markers of actual breast cancer. An important distinction must be made between using breast epithelial cells for the purpose of diagnosis versus the use of the cells as a measure of risk assessment. At the present time, these cells are best used as an enhancement to risk assessment, not as an independent diagnostic tool. Therefore, measures of sensitivity and specificity must be defined in relation to the risk assessment goals of breast epithelial cell evaluation.

Using Ductal Fluid to Explore Carcinogenesis

The paths to carcinogenesis appear to be varied and numerous. Only by viewing the process as a work in progress will researchers develop interventions that may allow for true cure or prevention. As the majority of breast cancer cases are not the result of known germline mutations, an understanding of the genetic and epigenetic events that lead to malignancy is necessary to further the creation of new treatment modalities. This understanding may be advanced by viewing cells to sort out true precursors from benign changes. Access to breast epithelial cells via the nipple orifices or through periareolar FNA is pivotal for studying women who have developed breast cancer as well as those who have not developed it. Perhaps the study of changes in breast epithelial cells over time will allow researchers to begin to specify when premalignant changes take place and the events related to those changes. The methods outlined in this article for obtaining breast epithelial cells may determine when proliferative cells progress to something more ominous or regress back to normal. The carcinogenic continuum may be illuminated by viewing cytologic or molecular changes over time that are correlated with cancer development.

Reevaluating the use of current breast cancer risk assessment models by incorporating a more biologic component may enable healthcare professionals to more accurately assess risk. Nipple aspiration and ductal lavage are important adjuvants to risk assessment that could be performed easily in an outpatient setting. RNs and advanced practice nurses who work in the area of breast cancer risk assessment could perform these procedures safely and competently and inform patients regarding results in the context of individual risk assessment. Currently, nurse practitioners are trained by surgeons to perform ductal lavage and nipple aspiration. Institution-specific protocols are developed jointly by nurse practitioners and surgeons and guide practice. The skill set required is similar to that of placing an IV catheter.

Nipple aspiration, ductal lavage, and periareolar FNA are tools that hold great promise for exploring the breast carcinogenesis process. Through the observation of cellular and molecular abnormalities, opportunities for intervening in carcinogenesis will be revealed.

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Strengths and Limitations of Breast Cancer Risk Assessment

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Purpose/Objectives: To evaluate current definitions of breast cancer risk and breast cancer risk assessment models, including the Gail, Claus, and BRCAPRO models, and discuss potential markers to enhance and standardize individual risk assessment.

Data Sources: Published articles, conference proceedings, and textbooks.

Data Synthesis: Defining high risk for breast cancer development is explored, and options for high-risk women are discussed. The risk factors frequently used for risk evaluation, including age, age at menarche, age at first live birth, past history of breast biopsy, family history of breast cancer, and the presence of atypical hyperplasia, are reviewed.

Conclusions: Current models of breast cancer risk assessment are limited. Exploring the progression from healthy tissue to malignancy through techniques such as fine needle aspiration, ductal lavage, and nipple aspiration may lead to more precise individualized risk prediction.

Implications for Nursing: More accurate information regarding personal breast cancer risk is necessary. Oncology nurses may facilitate the use of appropriate tools that provide the most individualized risk assessment.

Key Points . . .

- Assessing individual breast cancer risk has not been articulated in the United States despite an abundance of research devoted to risk factors.
- Currently employed risk assessment tools include the Gail model, the Claus model, and BRCAPRO.
- Exploring biologic markers such as atypical hyperplasia using minimally invasive methods (e.g., fine needle aspiration, ductal lavage, nipple aspiration) may enhance risk prediction.

Goal for CE Enrollees:

To enhance nurses' knowledge about breast cancer risk factors, risk assessment models, and potential areas for refinement.

Objectives for CE Enrollees:

1. Summarize the impact of known risk factors on the development of breast cancer.
2. Discuss the strengths and limitations of currently used breast cancer risk assessment models.
3. Describe the potential role of pathologic information in more precisely determining breast cancer risk.

Fear of developing breast cancer is well founded among women in the United States. Breast cancer is the leading cause of death among women aged 35–50 years and the second-leading cause of death in women older than 50 years (Jemal et al., 2005). Approximately 40,000 women will die from this disease in the United States in 2005. Refining the science of breast cancer risk assessment has become more important with the availability of genetic testing for mutations associated with an increased risk of breast cancer development and the manufacture of medications to reduce breast cancer risk (Hollingsworth, Nall, & Dill, 2002).

A standardized algorithm for breast cancer risk assessment is not available at this time in the clinical setting. Women are categorized as either having possible genetic or hereditary risk or as having risk factors unrelated to a family history of breast cancer. Genetic testing is limited as a risk assessment tool because only a small percentage of women carry known genetic mutations that result in an increased risk of breast cancer development. Mathematical models calculate probabilities of developing breast cancer over specified periods of time; however, the factors included in the models contribute a relatively small degree of risk for the eventual development of breast cancer. Hollingsworth et al. (2002) suggested that

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tissue- or serum-based strategies should be the next step in refining risk assessment, given that 70% of women who develop breast cancer have no identifiable risk factors.

Addressing inadequacies in breast cancer risk assessment may help to illuminate warning signs to women and healthcare providers as to who is at greatest risk for breast cancer development. This article will discuss risk assessment currently undertaken using the Gail and Claus models. In addition, the BRCAPRO program for assessing the probability of having known breast cancer genetic mutations will be discussed. Significant risk factors used in the clinical setting to determine risk will be outlined, as well as prevention options available to women deemed high risk. Abnormal epithelial breast cell cytology will be discussed as a potentially important risk factor to enhance current prediction models.

The Concept of High Risk

Defining High Risk

When is a woman at high risk for developing breast cancer? The generally agreed-upon risk factors currently used in various combinations in risk assessment models include being older than 65 years, experiencing early menarche (before 12 years of age), being nulliparous or having a first child after age 30, having a history of breast biopsy, and having a family history of breast cancer (Singletary, 2003). Radiation exposure at a young age (i.e., < 12 years) or as a treatment for Hodgkin disease also is associated with a higher risk of breast cancer development; however, it is not used as a risk factor in current risk assessment models (Clemons, Loijens, & Goss, 2000). The presence of atypical hyperplasia in breast tissue or fluid samples as a risk marker has shown significance in several studies (Fabian et al., 2000; Wrensch et al., 2001). Various techniques to obtain this finding through histology and cytology have been discussed in greater detail in another article (Baltzell, Eder, & Wrensch, 2005). Other factors contributing smaller degrees of risk for breast cancer development include drinking more than two alcoholic beverages per day, having a high body mass index in women older than 55 years, using hormone replacement therapy, and experiencing menopause after 55 years of age. Singletary succinctly listed the risk factors for breast cancer development (see Table 1). As more of these risk factors are present, the chance of developing breast cancer increases. The presence of a mutated *BRCA1* or *BRCA2* gene is currently the generally agreed-upon definition of high risk for breast cancer development. Multiple first-degree relatives with breast cancer and no mutated *BRCA1* or *BRCA2* gene in a woman's family history may suggest high-risk status, perhaps related to unknown genetic mutations.

If high risk was defined as a woman who has risk factors carrying a relative risk of greater than 2 (relative risk is the ratio of breast cancer risk among women with identified risk factors to the risk of breast cancer among women without those identified risk factors), then risk factors such as age, past personal history of breast cancer, lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), biopsy findings of hyperplasia with atypia, atypia with a positive family history of breast cancer, first-degree relative with premenopausal breast cancer, more than two first-degree relatives with breast cancer, and known *BRCA1* or *BRCA2* mutations would provide information correlated with high risk. However, the majority of women seen in the clinical setting will not have information about their cellular or genetic risk factors (i.e., LCIS, DCIS, hyperplasia with atypia, *BRCA1* and *BRCA2* mutations). Obtaining information about these cellular or genetic risk factors may lead to a more concise and accurate definition of "high risk."

Accurate risk assessment is becoming increasingly important as potential prevention options, particularly prophylactic surgery and chemoprevention (Singletary, 2003), become available; however, these options are accompanied by their own set of risks. A decision to proceed with prophylactic surgery or chemoprevention should be made with as precise an assessment as possible. Because each of the currently available assessment tools uses different variables to assess risk, a precise definition is elusive. According to Verp, Cummings, and Olopade (2001), most cancers develop as a result of a combination of genetic and environmental factors. Despite years of research dedicated to articulating the risk factors leading to breast cancer development, no model completely calculates a woman's risk with great accuracy, with the exception of genetic testing indicating the presence of a *BRCA1* or *BRCA2* mutation (Winer, Morrow, Osborne, & Harris, 2001). Even genetic testing models are limited, given that they are based on very few of the possible mutations that increase breast cancer risk and are only definitive in families in which these mutations have been demonstrated (Berry et al., 2002).

Hamolsky and Facione (1999) described the importance of assisting women in making realistic appraisals of their personal risks. They reported that breast cancer risk estimates are misleading for many women because each woman has her own unique circumstances. According to Kelly (2000), although most women have beliefs regarding the cause of breast cancer, not all of those beliefs fit with current scientific findings. Women consistently overestimate their risk of developing breast cancer, which can lead to screening avoidance and psychological morbidity (Armstrong, Eisen, & Weber, 2000; Black, Nease, & Tosteson, 1995). Not every woman who has all of the currently recognized risk factors will develop breast cancer; therefore, more accurate risk assessment tools must be developed. Given that prophylactic surgery or chemopreventive drugs are the currently available breast cancer prevention choices, a woman must feel confident that her risk assessment is as complete as possible.

Breast Cancer Prevention Options

In the clinical setting, a limited number of breast cancer prevention options are available for women determined to be at extremely high risk for developing breast cancer (i.e., *BRCA1* or *BRCA2* mutations, a strong family history of breast cancer in first-degree relatives). These options include prophylactic surgery, chemopreventive drugs, and lifestyle modifications. If an extensive family history of breast cancer is found, genetic counseling or testing, if appropriate, should be offered to ascertain whether a *BRCA1* or *BRCA2* mutation is present. Although high penetrance genes are thought to account for only 10%–20% of breast cancers, the risk of developing breast cancer in the presence of these genes is high (Hamolsky & Facione, 1999).

Prophylactic mastectomy is associated with a risk reduction of more than 90% in women with strong family histories of breast cancer (Hartmann et al., 1999). The risk reduction associated with this procedure was similar for women with a strong family history and a subset of women with positive

Table 1. Risk Factors for Breast Cancer

Risk Factor	Category at Risk	Comparison Category	Relative Risk
Alcohol intake	2 drinks per day	Nondrinker	1.2
Body Mass Index	80th percentile, age 55 or greater	20th percentile	1.2
Hormone replacement therapy with estrogen and progesterone	Current user for at least 5 years	Never used	1.3
Radiation exposure	Repeated fluoroscopy	No exposure	1.6
	Radiation therapy for Hodgkin's disease	No exposure	5.2
Early menarche	Younger than 12 years	Older than 15 years	1.3
Late menopause	Older than 55 years	Younger than 45 years	1.2–1.5
Age at first childbirth	Nulliparous or 1st child after 30	1st child before 20	1.7–1.9
Current age	65 or older	Less than 65	5.8
Past history of breast cancer	Invasive breast carcinoma	No history of invasive breast carcinoma	6.8
Other histologic findings	Lobular carcinoma in situ	No abnormality detected	16.4
	Ductal carcinoma in situ	No abnormality detected	17.3
Breast biopsy	Hyperplasia without atypia[a]	No hyperplasia	1.9
	Hyperplasia with atypia	No hyperplasia	5.3
	Hyperplasia with atypia and positive family history	No hyperplasia, negative family history	11.0
Cytology (fine-needle aspiration, nipple aspiration fluid)	Proliferation without atypia[a]	No abnormality detected	2.5
	Proliferation with atypia	No abnormality detected	4.9–5.0
	Proliferation with atypia and positive family history	No abnormality detected	18.1
Family history	1st-degree relative 50 years or older with postmenopausal breast cancer	No 1st- or 2nd-degree relative with breast cancer	1.8
	1st-degree relative with premenopausal breast cancer	No 1st- or 2nd-degree relative with breast cancer	3.3
	2nd-degree relative with breast cancer	No 1st- or 2nd-degree relative with breast cancer	1.5
	Two 1st-degree relatives with breast cancer	No 1st- or 2nd-degree relative with breast cancer	3.6
Germline mutation	Heterozygous for *BRCA1*, age < 40	Not heterozygous for *BRCA1*, age < 40	200.0[b]
	Heterozygous for *BRCA1*, age 60–69	Not heterozygous for *BRCA1*, age 60–69	15.0[b]

[a] There is controversy over whether pathologic hyperplasia detected in breast biopsy samples is directly equivalent to cytologic hyperplasia detected in samples obtained through FNA [fine needle aspiration] or nipple aspiration.

[b] Begg (2002) has suggested that these relative risks are subject to ascertainment bias and may overestimate the true risk associated with germline mutations in BRCA genes.

Note. From "Rating the Risk Factors for Breast Cancer" by S.E. Singletary, 2003, *Annals of Surgery, 237,* p. 475. Copyright 2003 by Lippincott Williams and Wilkins. Reprinted with permission.

BRCA1 and *BRCA2* mutations. Although genetic testing is not suggested routinely for screening, a detailed family history indicating many relatives with breast or ovarian cancers may warrant offering genetic counseling. If a woman is found to be positive for genetic alterations of genes *BRCA1* or *BRCA2,* prophylactic mastectomy may be recommended. Love, Newcomb, and Trentham-Dietz (2002) recognized the magnitude of suggesting such a prevention strategy by stating, "In the absence of clinically applicable comprehensive risk models for individual patients, indications for prophylactic mastectomy must be strong and specific" (p. 210).

The removal of a woman's ovaries, or prophylactic oophorectomy, has been effective in reducing breast cancer risk in women with a known *BRCA1* or *BRCA2* mutation. Removing the ovaries in premenopausal women diminishes the amount of estrogen circulating that can stimulate breast cancer cells. When this source of estrogen is eliminated in women with genetic mutations known to increase risk of breast cancer development, risk has been reduced by approximately 50% (Olopade & Artioli, 2004).

Chemoprevention is described as "the use of specific natural and synthetic chemical agents to reverse or suppress carcinogenesis and prevent the development of invasive cancer" (Hamolsky & Facione, 1999, p. 427). At present, the agents used for chemoprevention are a group known as selective estrogen receptor modulators (SERMs). Tamoxifen is the most widely prescribed SERM, and raloxifene currently is being evaluated for its effectiveness in preventing breast cancer development. SERMs act as estrogen agonists in some tissue (e.g., bone, endometrial) and as estrogen antagonists in other tissue (e.g., breast) (Brinton, Lacey, & Devesa, 2002). In the National Surgical Adjuvant Breast and Bowel Project (NSABP), a 49% lower risk of breast cancer was found in a tamoxifen-treated group versus a placebo-treated group (Fisher et al., 1998). Differences were apparent in groups within various studies; in a trial at the Royal Marsden Hospital, Eeles and Powles (2000) found that

SERMs were less effective in women with *BRCA1* and *BRCA2* mutations. Fisher et al. reported that the greatest risk reduction was in women with atypical hyperplasia. Risks associated with taking SERMs include stroke, deep vein thrombosis, and uterine cancer. Brinton et al. noted that although the overall results of SERM trials are informative, the analyses are less useful to individuals and their clinicians trying to make informed decisions regarding the appropriateness of this prevention strategy. That is, clinical guidelines are not yet clear about the recommendation of SERMs for breast cancer prevention.

Lifestyle changes have been examined in an effort to determine which may modify breast cancer risk. Dietary fat has been studied extensively as a risk factor for breast cancer development. According to Kushi and Giovannucci (2002), recommendations to reduce fat intake to prevent cancer risk are unwarranted. Drake (2001) reported that female joggers were less likely to develop breast cancer than those who did not jog. In another study, lifelong physical activity was potentially useful in reducing breast cancer risk (Bernstein, Henderson, Hanisch, Sullivan-Halley, & Ross, 1994). Physical activity in young women is associated with delayed menarche and anovulatory cycles, perhaps reducing overall lifetime exposure to estrogen. Although studies have not found a highly significant association between lifestyle variables and breast cancer prevention, a reduced-fat diet and increased exercise may be beneficial in regard to other diseases (e.g., cardiovascular disease). Love et al. (2002) created a table of possible primary prevention strategies categorized by age group (see Table 2). These interventions relate to the timing of breast tissue development and the role of hormonal changes leading to breast cancer susceptibility but do not necessarily include truly feasible or desirable modifications or programs for women. To recommend breast cancer prevention strategies, a comprehensive breast cancer risk assessment is necessary.

Table 2. Primary Prevention Interventions Most Important at Different Ages

Age	Primary Prevention Interventions
Preadolescence and adolescence	Limit chest and breast radiation Tobacco avoidance Regular exercise Avoid excessive calories and weight gain Increase fruits and vegetables: carotenoids and folic acid
Childbearing years	Early first full-term pregnancy Lactation, for long duration Avoid weight gain Regular exercise No or limited alcohol
In the 40s	Avoid weight gain Weight loss Regular exercise *The following interventions are most appropriate for women with extensive family history of breast cancer or known* BRCA1 *or* BRCA2 *mutations:* Prophylactic oophorectomy Prophylactic mastectomy SERM therapy
Menopausal years	Avoid weight gain Weight loss Regular exercise Limit estrogen replacement therapy *The following intervention is most appropriate for women with extensive family history of breast cancer or multiple identified breast cancer risk factors:* SERM therapy

SERM—selective estrogen receptor modulator

Note. From "Prevention of Breast Cancer" by R.R. Love, P.A. Newcomb, and A. Trentham-Dietz in *Cancer of the Breast* (5th ed., p. 218) by W.L. Donegan and J.S. Spratt (Eds.), 2002, Philadelphia: Saunders. Copyright 2002 by Elsevier. Reprinted with permission.

Risk Factors

Age, age at menarche, age at first live birth, family history of breast cancer, past history of breast biopsy, and the presence of atypical hyperplasia are risk factors that can be taken into account when assessing breast cancer risk. Table 3 summarizes the potential modifiability of these risk factors.

Age

Of all the commonly used risk factors to predict breast cancer, increasing age is believed to have the most significance (Winer et al., 2001). In more than 50% of women diagnosed with breast cancer, increasing age is the only identifiable risk factor (Madigan, Ziegler, Benichou, Byrne, & Hoover, 1995). Risk of breast cancer development increases steadily until age 70, at which point risk actually declines (Kelly, 2000). The commonly quoted 1 in 8 risk is derived from the addition of age-stratification risk numbers. Women aged 20–50 years have a 2% risk of breast cancer development (1 in 50), women aged 50–70 years have a 6% risk of breast cancer development (1 in 17), and women aged 70–80 years have a 3% risk (1 in 33) (Kelly). These are generalized risk numbers that cannot be used effectively for individual risk assessment. In nonhereditary breast cancers, the increased risk of breast cancer with advancing age may come more from "wear and tear" on genetic material, providing an opportunity for mutations to occur or from decreased immune surveillance. Recent statistics are listed in Table 4 and show the increased number of diagnoses as women age (Jemal et al., 2005).

Age at Menarche

Risk assessment often categorizes age at menarche as less than 12 years or more than 15 years, representing higher versus lower risk, respectively. If lifetime exposure to estrogen is associated with risk determination for breast cancer, then the number of actual cycles an individual has provides important estrogen exposure information. Age at menarche has received more attention in recent years because of observations of earlier onset of puberty in the United States (Lee, Guo, & Kulin, 2001). The combinations of higher fat and protein diets and effective disease control are believed to have had an impact on lowering the age of menarche (Henderson, Pike, Bernstein, & Ross, 1996). MacMahon et al. (1982) reported that establishment of ovulatory cycles and increased hormone levels found in women who experienced early menarche play a role in promoting breast cancer risk. Henderson et al. suggested that for women of equivalent age, those with more than 40 years of menstruation have twice the risk of those with fewer than 30 years of menstruation. Strategies for decreasing risk may

Table 3. Summary of Risk Factor Modification Feasibility

Risk Factors	Risk Modifiable?	Risk Modifiable at Age of Concern[a]	Advantages	Disadvantages
Age	No	No	Not applicable	Not applicable
Age at menarche	Possibly	No	Encouragement of increased exercise and lifelong healthy habits	Adolescence is the time of increased body image distortion and onset of eating disorders. The effect on other disease development is unknown.
Age at first live birth	Yes	No	Could confer a protective period postpregnancy at critical time for breast carcinogenesis	Economic instability associated with young maternal age may create other health issues that are more threatening than breast cancer development.
Past history of breast biopsy	Partially	No	Obtain information related to high-risk cellular abnormalities via less invasive methods (e.g., fine needle aspiration, nipple aspirate fluid, lavage).	Less invasive methods are not commonly practiced; accurate pathology reading is crucial for risk information.
Family history of breast cancer	No	No	Not applicable	Not applicable
Atypical hyperplasia	Unknown	Possibly[b]	Not applicable	Not applicable

[a] Age of concern is defined as the age at which risk for breast cancer development increases significantly. For purposes of this table, age 40 begins the "age of concern" based on the probability increase from 1 in 228 (age birth to 39) to 1 in 24 (age 40–59).

[b] Petrakis et al. (1996) found an increase in cytologic detection of epithelial hyperplasia in breast fluids after increased consumption of soy protein in a small study of women aged 30–58. This indicates the possibility of exogenous influences in altering the progression of atypical hyperplasia.

include looking at adolescence as an effective intervention age. Encouraging increased amounts of exercise and healthy eating habits may influence menarche onset by a small margin; however, each year of menarche delay may provide a significant decrease in later breast cancer risk. In addition to the benefit of fewer menstrual cycles resulting in decreased estrogen exposure in the breast tissue, exercise and healthy eating may contribute to decreased weight gain in adulthood. Adipose tissue is a major source of estrogen in postmenopausal women. Weight loss and low body mass index are associated with a decreased risk of breast cancer in postmenopausal women; however, this type of advice should be given cautiously. Recommending "thinness" to an adolescent girl may be associated with the development of eating disorders such as anorexia nervosa and bulimia (Martin & Ammerman, 2002). In addition, the burden of possible breast cancer development should not be added to adolescent worries, particularly if the timing of menarche can be altered only by radical shifts in lifestyle.

Age at First Live Birth

Chie et al. (2000) compared age at first pregnancy for breast cancer cases and controls and found a modest increased risk in breast cancer development (odds ratio = 1.07, confidence interval = 1.01–1.13) for each five-year increase in age at first full-term pregnancy. MacMahon et al. (1970) reported that women with their first full-term pregnancy before age 20 had a third of the breast cancer risk compared with women having their first full-term pregnancy after age 35. A short-term increased risk of breast cancer development may occur after pregnancy at any age; however, mammary cells become differentiated after this risk period, resulting in less susceptibility to carcinogenesis. This increased risk period is believed to last approximately 10 years (Bruzzi et al., 1988). An early pregnancy allows for mammary cell differentiation at an early age in a woman's reproductive life, perhaps conferring a protective effect during later high-risk years. Brinton et al. (2002) found the protective effect of early pregnancy only with full-term pregnancy. Singletary (2003) suggested that this is because of cell differentiation in preparation for lactation in the later stages of pregnancy. Brinton et al. also reported that nulliparous women and women who give birth around age 30 share a similar risk of breast cancer development. A full-term pregnancy after age 30 is associated with higher risk than nulliparity, possibly as a result of the increased risk period immediately after pregnancy. Brinton et al. speculated that already initiated cells may progress during the short-term high-risk period following later-age pregnancy. Because the protective effect of pregnancy is associated with maternal age of less than 20 years of age, it is unlikely to be a risk factor that is altered easily. However, the social trend toward later maternal age at pregnancy is continuing in North American societies (Lee et al., 2003), but changing reproductive choice, as suggested by Love et al. (2002), is unrealistic in any risk intervention strategy.

Table 4. Advancing Age and Corresponding Increase in Breast Cancer Rates

Age (Years)	% Diagnosed With Breast Cancer	Actual Number of Cases per Interval
0–39	0.4	1 in 228
40–59	4.0	1 in 24
60–79	7.0	1 in 14
Lifetime risk[a]	12.0	1 in 8

[a] With each age interval passed without a breast cancer diagnosis, risk for that category should be subtracted from subsequent age intervals (Kelly, 2000).

Note. Based on information from Jemal et al., 2005.

Past History of Breast Biopsy

According to Page et al. (1978), women with a history of breast biopsy have an elevated risk of approximately twice the general population for future breast cancer development. This

is because of the underlying presence of benign breast disease, which has been found to be significantly associated with breast cancer development (Webber & Boyd, 1986). Breast biopsy history has been included in the Gail risk model as an important risk factor. Kelly (2000) argued against using the number of biopsies in a risk model because some, but not all, benign breast disease leads to biopsy, limiting its usefulness as a risk marker. Hughes, Mansel, and Webster (2000) wrote, "There is no reason to believe that the clinical presentations that induce a surgeon to perform a biopsy will be associated with high-risk pathology as most of the hyperplastic lesions with atypia are found incidentally at biopsy for a condition such as dominant nodularity" (p. 255). Is the fact that a woman had a biopsy important in risk assessment? Using the actual results of the biopsy may be more informative, but only if hyperplasia or atypical hyperplasia is present. Page et al. investigated the link between histologic changes present in breast tissue and breast cancer risk and concluded that benign breast disease is not necessarily associated with increased cancer risk; however, histologic changes defined as epithelial proliferative disease may distinguish high-risk groups from women with general population risk. Winer et al. (2001) noted that most breast biopsies result in nonproliferative disease findings. Using the number of biopsies in a risk model would lead to an overestimation of risk based on this information. Refining the concept of breast biopsy numbers is necessary for value in clinical decision making. Suggesting biopsies for large populations of at-risk women is unrealistic and cost prohibitive. Determining the presence of abnormal proliferative changes through less invasive methods that may lead to biopsy might improve the prediction value and specificity of this factor. Perhaps the incorporation of pathology findings (via biopsy, fine needle aspiration, lavage, or nipple aspiration) is more essential for enhanced risk assessment.

Family History of Breast Cancer

A family history of breast cancer is associated with a significant increase in breast cancer risk; however, only 5%–10% of breast cancers are believed to have strong hereditary origins (Winer et al., 2001). In addition, Winer et al. wrote that "family history is a heterogeneous risk factor with different implications depending on the number of relatives with breast cancer, the exact relationship, the age at diagnosis, and the number of affected relatives" (p. 1652). A person with multiple relatives diagnosed with breast cancer at an early age is at greater risk than a woman with one relative diagnosed at a postmenopausal age. Kelly (2000) listed the following indications that hereditary cancers may be present: young age at diagnosis, one person diagnosed with several different cancers, cancers present in two or more generations, and three or more cancers found in close relatives. Complicating the family history is that shared environment might contribute to disease development in all family members, independently of any inherited genetic mutation.

Two tumor suppressor genes have been identified that are associated with true genetic risk of breast cancer development. Located on chromosome 17 is *BRCA1,* and on chromosome 13 is *BRCA2* (Winer et al., 2001). Mutations in either of these genes correlate with a 50%–85% lifetime chance of developing breast cancer. Additionally, these mutations can be passed down by either the mother or father. The large size of *BRCA1* and *BRCA2* makes genetic testing prohibitively expensive and unreasonable for large populations (Winer et al.). The cost of testing for a BRCA mutation was more than $2,500 in 2000 (Kelly, 2000). Also, all *BRCA1* and *BRCA2* mutations are not the same. Researchers have been unable to determine whether mutations in different locations on the gene convey the same level of risk. At this time, a positive genetic test means that a person might be at increased risk for breast cancer development; however, a negative test cannot rule out the possibility of another unknown mutation. Counseling a woman in regard to genetic testing involves a complex and complete screening process, including the discussion of breast cancer prevention strategies available in the event of a positive test. Other considerations regarding genetic counseling include the need for privacy and availability of qualified genetic counselors to guide future decisions affected by the presence of *BRCA1* and *BRCA2* mutations.

Atypical Hyperplasia

Recent studies have demonstrated a significant relationship between the presence of atypical hyperplasia in breast tissue or fluid samples and increased breast cancer risk (Fabian et al., 2000; Wrensch et al., 2001). Cytologic and histologic attributes associated with atypical hyperplasia include (a) an increase in cellular mitotic activity, (b) nuclear enlargement, (c) irregular nuclear borders, (d) nuclear hyperchromasia, (e) involvement of two or fewer ductal sections, and (f) foci measuring less than 2 mm (Rosen, 2001). Cells may be obtained by a number of methods, including breast biopsy, fine needle aspiration, ductal lavage, and nipple aspiration; however, results may vary based on the method of cell extraction chosen. Dupont and Page (1985) reexamined breast biopsies of 3,303 women after 17 years and found that women with atypical hyperplasia had a relative risk for invasive breast cancer of 5.3, with an increased relative risk of 11 for women with atypical hyperplasia and a positive family history. Inspired by an early study (Papanicolaou, Holmquist, Bader, & Falk, 1958), Sartorius, Smith, Morris, Benedict, and Friesen (1977) developed a nipple aspiration device to obtain breast fluid from 1,706 women. Fluid was obtained in approximately 50% of the cohort, and study results indicated a significant relationship between the presence of atypia and underlying breast cancer. Fabian et al. used fine needle aspiration to examine cells for the presence of atypical hyperplasia and determined that cytomorphologic findings of atypical hyperplasia are useful in evaluating short-term breast cancer risk. In several studies. abnormal cellular cytology in breast fluid was associated with an increased risk of breast cancer (Wrensch et al., 1992, 2001; Wrensch, Petrakis, King, Lee, & Miike, 1993). King, Chew, Petrakis, and Ernster (1983) documented the high correlation between atypical hyperplasia found in nipple aspirate fluid and atypical proliferative disease found in breast biopsy. This study confirmed the feasibility of using any of the available methods (biopsy, fine needle aspiration, ductal lavage, or nipple aspiration) to examine abnormalities associated with higher breast cancer risk. If cytologic and histologic methods of obtaining cells yield equally accurate information, choosing less invasive and costly procedures (e.g., fine needle aspiration, nipple aspiration) would allow for broader use of this marker for risk assessment. Dooley et al. (2001) concluded that ductal lavage is safe and well tolerated by most women, as well as a source of many breast epithelial cells for analysis. O'Shaughnessy (2001) stated that ductal lavage was a promising risk assessment tool. In addition, a number of breast cancer specialists recommended incorporating breast fluid findings into the breast cancer risk profile (Goodman, 2002).

Current Models of Breast Cancer Risk Assessment

Overview

For the purposes of this article, a breast cancer risk assessment model refers to mathematical models that calculate actual risk of breast cancer development as well as genetic tests (e.g., BRCAPRO) that examine known breast cancer gene mutations (e.g., *BRCA1, BRCA2*). The most commonly employed breast cancer risk assessment models currently are the Gail model and the Claus model (mathematical models) and BRCAPRO, which is used to evaluate the possible presence of genetic mutations associated with increased risk of breast cancer development. The Tyrer-Cuzick model has been developed to address concerns and limitations of currently used models. This model incorporates the likelihood of the presence of genes predisposing one to breast cancer, as well as personal risk factors (Tyrer, Duffy, & Cuzick, 2004). However, this model has not been validated independently (Amir et al., 2003). Euhus (2001) stated that an understanding of the principles used in each of these models is essential for healthcare professionals engaged in risk management counseling. MacDonald (2002) suggested that all healthcare providers will come in contact with a woman who has a family history of breast cancer at some point, given the prevalence of this disease. Risk assessment models are not used uniformly in clinical practice, making the accuracy of each woman's risk assessment a function of her provider's knowledge. Regarding healthcare providers, Kelly (2000) reported, "Many have a general knowledge of breast cancer risks, but few make it their specialty, have the time to keep up with all the latest developments in this area, or are aware of all whose risk might be increased" (p. 174).

Gail Model

Gail et al. (1989) developed a mathematical model for risk assessment of invasive and in situ breast cancer using information from 284,780 Caucasian women participating in the Breast Cancer Detection Demonstration Project from 1973–1980. This was a first attempt to refine population characteristics and based risk assessment on subgroups of women with varying risk factors, including age, age at menarche, number of prior breast biopsies, age at first live birth, and number of first-degree relatives affected with breast cancer. Relative risk was calculated for each of these risk factors; those relative risks (i.e., the probability of developing breast cancer in a given population) then were used to calculate absolute risk at five years from the time of assessment and a lifetime risk up to the age of 90. This model has been modified to include African Americans as well as Caucasians and uses invasive cancer as the only defined "breast cancer event" (Euhus, Leitch, Huth, & Peters, 2002). In addition, the presence of atypical hyperplasia has been added as a risk factor (Euhus, Leitch, et al.). The modified Gail model was used to qualify women for enrollment eligibility by the NSABP to assess the effectiveness of tamoxifen in preventing breast cancer development. Women with a five-year Gail score of more than 1.7% were designated "high risk" and qualified for participation in the tamoxifen study. In addition, this model was used for selection of candidates for the Study of Tamoxifen and Raloxifene trial comparing the effectiveness of tamoxifen versus raloxifene (Euhus, 2001).

Strengths of the Gail model include its attempt to adapt risk assessment from the general population to be more applicable to specific subgroups. In a study by Euhus, Leitch, et al. (2002), the Gail model was useful in specialized clinic settings, although it is criticized widely for not accounting for adequate family history information. The Gail model was developed prior to extensive genetic testing and now is thought to be most applicable to women without a strong family history suggestive of an inherited genetic mutation (Sakorafas, Krespis, & Pavlakis, 2002).

Criticisms of the Gail model are wide and varied, but it is limited by the characteristics of the data set used for its development. Kelly (2000) reported that the Gail model was problematic because (a) relative risk is not an accurate way to obtain absolute risk, (b) the number of biopsies included in the calculation is too simplistic (the pathology information obtained from the biopsy is more informative than the fact that a biopsy was performed), (c) all relevant family history is not included (i.e., grandparents and paternal history relatives are excluded), and (d) risk is overestimated in young women. Bondy and Newman (2003) found that the model has not been validated in African American women and stated their concern relative to enrollment and recruitment of African Americans in the ongoing NSABP trials. In addition to complaints regarding lack of validation for African Americans, no attempt has been made to validate the Gail model in other ethnic populations. The addition of atypical hyperplasia may enhance model accuracy; perhaps this would replace the number of biopsies with more useful biologic information.

Claus Model

In 1993, Claus, Risch, and Thompson published information on a model that incorporated extensive family history of cancer development. These data were obtained from the Cancer and Steroid Hormone Study, consisting of interviews of 4,730 confirmed breast cancer cases and 4,688 controls. The final model included breast cancer information on not only mothers and sisters but aunts and grandmothers as well. The development of the Claus model supported the notion that inherited genetic mutations might increase the risk of breast cancer and was a hint of a genetic component that would be elucidated further in the following five years (Euhus, 2001). The Claus model also addressed an inadequacy of the Gail model. The strength of the Claus model is its ability to incorporate the age of affected family members at diagnosis into the analysis. Since the discovery of *BRCA1* and *BRCA2* mutations, this information has taken on more importance, given that a woman with early onset of the disease is more likely to carry one of these mutations. However, the Claus model does have its own limitations: It does not include known breast cancer risk factors that are unrelated to family history of breast cancer, such as those included in the Gail model (Euhus). Therefore, the Claus model cannot be used among women without a family history of breast cancer. Because of the small sample size of African Americans in the original data set, final risk assessments did not include race. Other ethnicities were not addressed, probably because of the limited amount of information available for analysis. This model may be most helpful for women with a strong family history of breast cancer. Comparisons between the Gail and Claus model are shown in Table 5.

Table 5. Variables Used in the Gail and Claus Models

Variable	Gail	Claus
Age	Yes	Yes
First-degree family history (i.e., mother, sisters, and daughters)	Yes	Yes
Second-degree family history (i.e., aunts and grandmothers)	No	Yes
Age at onset in relatives	No	Yes
Age at menarche	Yes	No
Age at first live birth	Yes	No
Number of breast biopsies	Yes	No
Atypical hyperplasia	Yes	No
Race and ethnicity	Yes	No

Note. Based on information from McTiernan et al., 2001.

BRCAPRO

Unlike the Gail and Claus models of breast cancer risk assessment, BRCAPRO is used to determine the probability of having a genetic mutation (specifically *BRCA1* or *BRCA2*) associated with an increased risk of developing breast cancer. Although other genetic risk models exist, BRCAPRO is considered the most comprehensive (Allain, Gilligan, & Redlich, 2002). It is described as mathematically "intense" and uses Bayes theorem to answer the questions: "Given this pattern of affected and unaffected relatives, what is the probability that this individual carries a mutation in one of the BRCA genes? Given this BRCA gene mutation probability, what is the probability that this individual will develop breast cancer?" (Euhus, 2001, p. 228). The reliability of the calculation grows as more information is added to the model about the age and history of relatives with breast and ovarian cancer. Euhus wrote that the key to the usefulness of this model lies in knowing the underlying frequency of mutated genes in the population to which a patient belongs (e.g., European American, Eastern European Jewish).

BRCAPRO was found to be relatively accurate in predicting the presence of BRCA mutations in samples where the probability of penetrance was either very high (> 95%) or very low (< 5%) (Berry et al., 2002). BRCAPRO is a sensitive tool, missing only 15% of mutations present; however, Berry et al. did not determine whether this tool is useful in predicting which mutation carriers will develop breast cancer. Additional studies found that BRCAPRO more accurately identified possible mutations than experienced risk counselors (Euhus, Smith, et al., 2002). Limitations of the model include its underestimation of women's risk when familial clustering is unrelated to BRCA gene mutation (Euhus, 2001). Allain et al. (2002) listed lack of verification of family history as another limitation of this tool. BRCAPRO does not evaluate risk factors unrelated to family history (e.g., reproductive risk factors, presence of atypical hyperplasia). See Table 6 for a comparison of the three breast cancer risk assessment models.

Using Atypical Hyperplasia to Enhance Assessment Models

Most women who develop breast cancer do not have a known genetic mutation that indicates increased risk for the disease. How can more specific biologic information be obtained to refine breast cancer risk assessment? Perhaps examining breast epithelial cells (via lavage, nipple aspirate fluid, or periareolar fine needle aspiration) will illuminate cellular changes leading to cancer development. Daly and Ross (2000) stated that an understanding of the biologic progression from healthy breast epithelium to malignancy has been impeded by a lack of access to at-risk tissue for surveillance. Studies show atypical hyperplasia's contribution to increased risk in breast cancer development to be four- to fivefold in atypical hyperplasia, rising to anywhere from 11- to 18-fold in women with atypical hyperplasia and family history of breast cancer (Dupont & Page, 1985; Singletary, 2003). These relative risks are higher by a substantial margin than relative risks of currently accepted breast cancer risk factors such as age at menarche or age at first pregnancy. Increased emphasis should be placed on obtaining biologic markers of breast cancer risk that will allow for more accurate assessment of who is truly at risk for disease development. O'Shaughnessy (2001) wrote that more specific tools, such as ductal lavage to obtain cytologic information, are necessary to substratify women into useful risk assessment categories. Promising studies indicate that evaluating breast epithelium may yield important clues as to who may be at great risk for breast cancer (Fabian et al., 2000; Wrensch et al., 2001). This addition to risk assessment has become more feasible because data from less invasive means (nipple aspiration) provide

Table 6. Advantages and Disadvantages of the Gail, Claus, and BRCAPRO Models

Characteristic	Gail	Claus	BRCAPRO
Advantages	Accurately predicts the number of expected cases of breast cancer in large-scale clinical trials; incorporates nonfamily risk factors	Uses information from first- and second-degree relatives; incorporates age at diagnosis of affected family members	Most comprehensive estimate of genetic mutation risk; highly sensitive
Disadvantages	All relevant family history of breast cancer is not included; the model may overestimate risk in young women.	Does not include breast cancer risk factors other than family history	Underestimates risk in women with familial clustering unrelated to *BRCA1* and *BRCA2* mutations; does not evaluate risk factors unrelated to family history of breast cancer
High-risk definition	High risk is defined as a score of more than 1.7% within a five-year time period.	–	–
Most appropriate population	Women without a strong family history of breast cancer	Women with a strong family history of breast cancer	Women with a strong family history of breast or ovarian cancer

a degree of pathologic information on par with breast biopsy (King et al., 1983). In the past, cytologic information has been available only for a limited number of at-risk women, which has made the inclusion of atypical hyperplasia information sporadic in risk assessment models. Incorporating these findings into regular risk assessment may help to further specify who requires more aggressive, invasive follow-up. At present, assessment of atypical ductal hyperplasia may be one of the risk assessment tools with the most potential.

Conclusion

The mathematical Gail and Claus models may benefit from the addition of a serum- or tissue-based biologic marker of breast cancer risk. As these models are used currently, certain women's risk of breast cancer development may be overestimated or underestimated. Risk factors used in these models are largely unmodifiable, either practically or ethically. In addition, many of the risk factors used for assessment contribute very small relative risks, making their importance in risk models questionable. The definition of who is at high risk for breast cancer development should be expanded and articulated. The development of breast cancer prevention options makes this articulation even more critical. Fisher et al.'s (1998) conclusion that tamoxifen was most beneficial in women with atypical hyperplasia suggested an important link between cytologic findings and benefit from prevention strategies. Studying cytologic and histologic proliferative patterns such as atypical hyperplasia may lead to the next step in refining risk assessment.

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1. Modification of breast cancer risk assessment techniques has become necessary because of
   a. New screening tests for genetic mutations associated with breast cancer.
   b. Clearer delineation of the environmental causes of breast cancer.
   c. New interventions that must be used immediately upon diagnosis of breast cancer.
   d. Novel diagnostic techniques that carry a lower risk during the workup for breast cancer.
2. Currently, most women who develop breast cancer exhibit how many risk factors?
   a. 0
   b. 1
   c. 2–3
   d. 4 or more
3. When assessing a woman's risk of developing breast cancer using current risk assessment models, which of the following would indicate increased risk?
   a. Menarche at 13 years of age
   b. History of radiation therapy for Hodgkin disease
   c. Being 55 years of age
   d. Never having had children
4. Currently, a woman is considered at high risk of developing breast cancer if she
   a. Used hormone replacement therapy.
   b. Carries a mutated *BRCA1* or *BRCA2* gene.
   c. Reached menopause after the age of 55.
   d. Has a history of undergoing breast biopsy.
5. When helping a woman at extremely high risk for developing breast cancer evaluate her options, which prevention option that is associated with the greatest reduction in this risk should be noted?
   a. Prophylactic oophorectomy
   b. Lifestyle changes
   c. Selective estrogen receptor modulator therapy
   d. Prophylactic mastectomy
6. For a woman with a strong family history of breast cancer, which breast cancer risk assessment model would be most appropriate to use?
   a. Study of Tamoxifen and Raloxifene
   b. Tyrer-Cuzick
   c. Claus
   d. Gail
7. Which commonly used risk factor is believed to play the most significant role in the development of breast cancer?
   a. Family history of breast cancer
   b. Age at first live birth
   c. Personal history of breast biopsy
   d. Increasing age
8. A history of breast biopsy is considered a risk factor for developing breast cancer because
   a. Abnormal breast cells released during biopsy have the propensity to spread into local tissue.
   b. Benign breast disease that leads to biopsy is significantly associated with cancer development.
   c. Stress associated with breast biopsy procedures stimulates breast cell malignant transformation.
   d. The majority of breast biopsy results leads to findings of proliferative breast disease.
9. Which of the following methods for obtaining breast epithelial cells is most feasible for use in a large breast cancer screening program?
   a. Incisional biopsy
   b. Nipple aspiration
   c. Excisional biopsy
   d. Nipple scraping
10. The Gail breast cancer risk assessment model would be most appropriate for evaluating women
    a. With a family history of cancers in two or more generations.
    b. Across a wide variety of ethnic and minority groups.
    c. Who appear to exhibit several noninherited risk factors.
    d. Younger than 40 years of age and premenopausal.
11. For a woman with multiple family members diagnosed with breast and ovarian cancer, which assessment model would be most helpful in estimating her breast cancer risk?
    a. Gail
    b. Claus
    c. BRCAPRO
    d. Tyrer-Cuzick
12. Which of the following factors has been found to most significantly increase a woman's relative risk of developing breast cancer?
    a. Atypical hyperplasia
    b. Age at menarche
    c. Nulliparity
    d. History of breast biopsy

13. When developing a breast health educational program for adolescent girls, which recommendation would be most appropriate to include?
    a. Maintain a thin body through a high-protein diet.
    b. Plan to breastfeed any children for at least one year.
    c. Take a multivitamin with minerals every day.
    d. Regularly engage in enjoyable physical activity.

14. The breast cancer risk factor that currently shows the most potential in the refinement of risk assessment tools is
    a. Genetic mutations beyond *BRCA1* and *BRCA2*.
    b. Atypical hyperplasia.
    c. Breast cell response to tamoxifen exposure.
    d. Number of breast biopsies.

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5. Contact hours will be awarded to RNs who successfully complete the program. Successful completion is defined as an 80% correct score on the examination and a completed evaluation program. Verification of your CE credit will be sent to you. Certificates will be mailed within six weeks following receipt of your answer/enrollment form. **For more information, call 866-257-4667, ext. 6314.**

Instructions: Mark your answers clearly by placing an "x" in the box next to the correct answer. This is a standard form; use only the number of spaces required for the test you are taking.

1. ❑ a ❑ b ❑ c ❑ d	2. ❑ a ❑ b ❑ c ❑ d	3. ❑ a ❑ b ❑ c ❑ d	4. ❑ a ❑ b ❑ c ❑ d	5. ❑ a ❑ b ❑ c ❑ d	6. ❑ a ❑ b ❑ c ❑ d	7. ❑ a ❑ b ❑ c ❑ d	8. ❑ a ❑ b ❑ c ❑ d	9. ❑ a ❑ b ❑ c ❑ d	10. ❑ a ❑ b ❑ c ❑ d
11. ❑ a ❑ b ❑ c ❑ d	12. ❑ a ❑ b ❑ c ❑ d	13. ❑ a ❑ b ❑ c ❑ d	14. ❑ a ❑ b ❑ c ❑ d	15. ❑ a ❑ b ❑ c ❑ d	16. ❑ a ❑ b ❑ c ❑ d	17. ❑ a ❑ b ❑ c ❑ d	18. ❑ a ❑ b ❑ c ❑ d	19. ❑ a ❑ b ❑ c ❑ d	20. ❑ a ❑ b ❑ c ❑ d

Name _____ Telephone # _____

Address _____ Last four digits of social security # _____

City _____ State _____ Zip _____

State(s) of licensure/license no(s). _____ ONS membership # _____

Program Evaluation	Not at all	Low	Medium	High
1. How relevant were the objectives to the CE activity's goal?	❑	❑	❑	❑
2. How well did you meet the CE activity's objectives (see page 605)?				
• Objective #1	❑	❑	❑	❑
• Objective #2	❑	❑	❑	❑
• Objective #3	❑	❑	❑	❑
3. To what degree were the teaching/learning resources helpful?	❑	❑	❑	❑

	Too basic	Appropriate	Too complex
4. Based on your previous knowledge and experience, do you think that the level of the information presented in the CE activity was	❑	❑	❑

5. How long did it take you to complete the CE activity? _____ minutes

❑ My check or money order payable to the Oncology Nursing Society is enclosed. U.S. currency only. (Do not send cash.)

After completing this form, mail it to: **Oncology Nursing Society, P.O. Box 3510, Pittsburgh, PA 15230-3510.**

For more information or information on the status of CE certificates, call 866-257-4667, ext. 6314.